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Gestational Alloimmune Liver Disease in a Neonate: A Case Report

Mousa Ahmadpour-kacho [1], Yadollah Zahedpasha [1], Samira Pournajaf [*1], Shahla Rahbar [2], Khadijeh Ebrahimi kiasari [2]

1. Non-Communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR Iran.
2- Clinical Research Development Unit of Amirkola Children's Hospital, Babol University of Medical Sciences, Babol, IR Iran.

*Corresponding Author: Dr. Samira Pournajaf;
Address: Non-Communicable Pediatric Diseases Research Center, No 19, Amirkola Children's Hospital, Amirkola, Babol, Mazandaran Province, 47317-41151, IR Iran.
Tel-Fax: +98 1132346963 E-mail: samirapournajaf@yahoo.com

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ABSTRACT

Background and Objective: Gestational alloimmune liver disease (GALD) is a rare hepatic disorder that begins during the intrauterine period with alloimmune mechanisms. The newborn shows signs of hyperbilirubinemia, hypoalbuminemia, and signs of liver failure. Because of the alloimmune mechanism, exchange transfusions and intravenous immunoglobulins are used as the treatment of choice.

Case Report: We present a 15-day-old male newborn with conjugated hyperbilirubinemia, mild skin darkening and poor feeding that progressed to coagulopathy, increased serum ferritin and liver failure. On clinical suspicion and after a biopsy, the patient was treated but died and the diagnosis of the disease was confirmed by autopsy. The baby died despite exchange transfusion in combination with intravenous immunoglobulin and necropsy confirmed the presence of blue granules in the panlobular and also within the Kupffer cells, in a specific iron staining consistent with the diagnosis of GALD.

Conclusion: Despite the fact that slightly darker skin in direct hyperbilirubinemia is due to phototherapy, a diagnosis of GALD should be considered in any infant with cholestasis and liver failure.

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Introduction

Gestational alloimmune liver disease (GALD) moreover known as neonatal hemochromatosis, is a rare hepatic disorder that starts through an intrauterine period with an alloimmune component requiring interaction between the maternal and fetal immune system [1, 2]. The onset of this disease is intrauterine and the newborn has the following signs and symptoms in the first few days of life. These signs include conjugated and unconjugated hyperbilirubinemia, hypoalbuminemia, coagulopathy, ascites, and liver failure.

Diagnosis is based on immunohistochemical features characteristic of alloimmune disease [3]. By utilizing MRI and seeking out additional hepatic iron deposits, the conclusion can be supported. Exchange transfusion (ET) and its combination with intravenous immunoglobulin (IVIG) is the current treatment of choice for infants with GALD. Studies have shown that a few babies respond to this treatment and recover, but numerous pass on [4, 5, 6].

Here we report a case of cholestasis in an infant with somewhat darker skin that was ultimately diagnosed as GALD. Accurate diagnosis in these patients, in addition to helping the current baby, may also help the next child, who is diagnosed in utero and treated with IVIG at the right time during pregnancy [7].

Case presentation

A 15-day-old male newborn (BW=2100 gr, GA=38wk, his parents are first cousins) was admitted for direct hyperbilirubinemia. He was born by emergency cesarean section due to IUGR, fetal stress and oligohydramnios and transferred to the neonatal intensive care unit due to respiratory distress and tachypnea at birth.

At first, the baby was admitted to another hospital, but due to jaundice, which did not respond to initial treatment and developed into direct hyperbilirubinemia, he was transferred to our center at the request of the family at 15 days of age for further diagnostic measures and treatment.

On initial clinical examination at our center, the patient presented with malnourished, wrinkled, suntanned to slightly dark skin, a thin face, icteric sclerae and pale conjunctivae. He was alert and had normal primitive reflexes. Heart and lung sounds were normal. On abdominal examination, the liver was found 2 centimeters below the subcostal margin, and the spleen could not be identified. The limbs and extremities were thin with normal mobility.

Initial laboratory data revealed anemia (hemoglobin 8.3 g/dl, hematocrit 22.4%), elevated C-reactive protein (100 mg/dl, NL R<6 mg/dl), normal electrolytes, blood calcium and glucose, normal aminotransferases, hypoalbuminemia (2 g/dl), and normal thyroid function tests were noted. Additionally, a total bilirubin of 5.8 mg/dl and a direct bilirubin of 4 mg/dl, a negative direct Coombs test and an adequate glucose-6-phosphate dehydrogenase (G6PD) were found. Pseudomonas aeruginosa grew in the patient's cerebrospinal fluid (CSF) sample, but CSF analysis, including cytology, glucose, and protein levels, was NL. No microbial growth was detected in the blood samples.

Considering the antibiotics used during the previous hospitalization (vancomycin and meropenem) and the antibiogram, the patient was treated with appropriate antibiotics and laboratory tests were continued: Ultrasonography of the liver showed normal size and parenchyma, intrahepatic and extrahepatic bile ducts, and a normal gallbladder. X-ray examination of the spine was normal. The serological test for toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex (TORCH) was negative and the polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was also negative. Metabolic tests, including amino acid chromatography by high-performance liquid chromatography and acylcarnitine profiling, and tests for organic acids in urine by gas chromatography-mass spectrometry revealed no pathological findings.

The consultant ophthalmologist reported no evidence of metabolic disease or TORCH infection, but a slightly elevated optic cup/disc ratio ratio was reported as a minor finding. The consulting pediatric cardiologist noted left ventricular dilatation and mild ischemic heart failure, mild

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atrial septal defect, and patent ductus arteriosus. A gastroenterologist was consulted and the necessary tests were ordered to rule out other causes for the direct hyperbilirubinemia and cholestasis, and vitamin supplements and the necessary medications were administered.

After submission of tests such as ferritin, ammonia, lactate, pyruvate, gamma-glutamyl transferase (GT), alpha1-antitrypsin, alpha-fetoprotein, fresh frozen plasma (FFP) and packed red blood cells were transfused depending on the coagulopathy and severe progressive anemia. During hospitalization, the patient's hemoglobin concentration dropped rapidly and significantly several times, so we had to transfuse packed cells several times (Figure 1). This was probably due to hemolysis.

The serum levels of ferritin, gamma-GT, alpha-fetoprotein, and alpha1-antitrypsin were 2775 ng/ml, 105 U/L, 2113 ng/ml, and 250 mg/dl, respectively (Table 1). Based on the elevated serum ferritin level, progressive coagulopathy, hypoalbuminemia, elevated transaminases, and slightly dark skin color, alloimmune gestational liver disease was considered as a provisional diagnosis and exchange transfusion was considered. At 22 days of age (one week after admission), intravenous immunoglobulin (IVIG) was immediately started as an adjunct therapy.

The liver biopsy was delayed due to a coagulopathy that could not be resolved by vitamin K injections and FFP and cryoprecipitate transfusions. However, once the coagulation status had stabilized, a liver biopsy and a biopsy of the oral mucosa were performed. Nevertheless, for technical reasons, the sampling was unsuccessful and the final diagnosis was confirmed by an autopsy of the postmortem liver specimen, indicating the presence of blue granules panlobular. The specific iron staining within the lobular and Kupffer cells was consistent with a diagnosis of GALD. During hospitalization, the patient had recurrent episodes of abdominal distension and feeding intolerance, poor feeding and lethargy and received supportive care. Despite ET and IVIG and supportive care, the disease progressed to cardiopulmonary arrest and the patient died despite full cardiopulmonary resuscitation. A postmortem liver autopsy was performed and the pathologist's diagnosis of GALD was confirmed (Figure 2).

Table 1. Abnormal laboratory findings

Test	Result	Unit
Hb	8.3	g/dl
Hct	22.4	%
Crp	100	mg/dl
Albumin	2	g/dl
Tot Bilirubin	5.8	mg/dl
Direct Bilirubin	4	mg/dl
Ferritin	2775	ng/ml
Gamma GT	105	u/l
Alfa Feto Protein	2113	ng/ml
Alfa1 Antitrypsin	250	mg/dl
Aminotransferases	At first, they were normal but gradually increased	

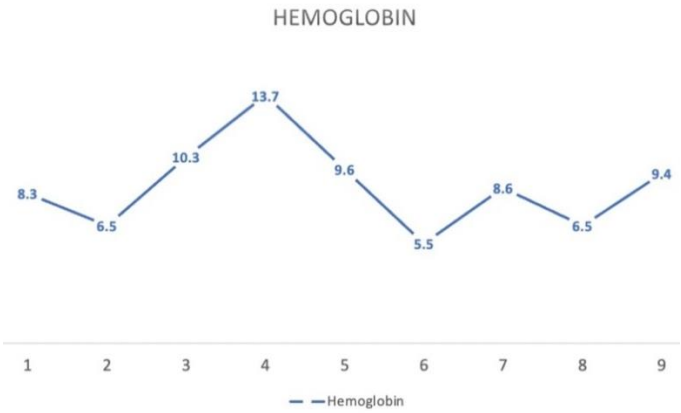

Figure 1. Changes in patients' hemoglobin during hospitalization

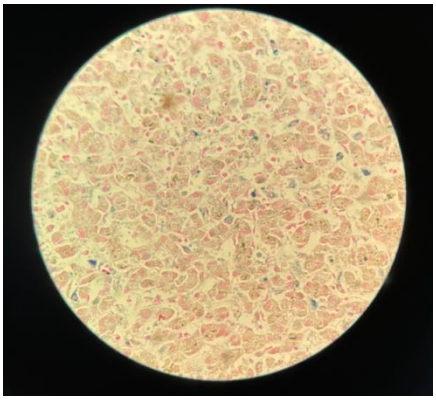

Figure 2. The presence of blue granules panlobular and also inside the Kupffer cells with specific iron staining, consistent with the diagnosis of GALD

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Discussion

This study reported on an infant who was treated for suspected GALD but died despite treatment, and the final diagnosis was not made until after the infant's death.

GALD is a rare liver disease that begins in utero and is associated with hyperbilirubinemia, hypoalbuminemia and severe coagulopathy. Currently, the treatment of choice in these patients is ET and its combination with IVIG [4-6]. This was done in our patient. It appears that the disease progressed normally in this patient and did not respond to conventional treatments.

Adhi Teguh Perma Iskandar and colleagues presented a newborn boy whose mother was suspected to have parvovirus infection. He was not vigorous at birth and GALD was clinically suspected on the basis of the prenatal history, severe clinical course, elevated liver enzymes and elevated serum ferritin levels on the first day of life. Immediately after the infant was born, IVIG was administered at a dose of 0.4 g/kg/day, and exchange transfusions were performed four times at 1, 3, 5, and 7 days of age [7]. The infant made significant progress in feeding and development and was discharged from the hospital at 26 days of age. Our patient was brought to us at 15 days of age and the ET was performed once at 22 days of age. Two days after the ET, the umbilical vein catheter was removed due to excessive abdominal distension and the patient's instability, which prevented us from performing the blood ET again. Perhaps the frequency of ET and the age of the baby compared to ours led to better outcomes.

Hendrik S. Fischer et al. reported on the clinical course and outcomes of 12 infants with suspected GALD who were treated early with ET as part of an 11-year descriptive cohort study. Of these 12 patients, 1 patient was diagnosed late (at 22 days of age) and 1 patient with severe acute liver failure at birth died. Others survived and had a favorable outcome of their liver disease [4]. Perhaps the delay in diagnosis due to late referral was due to the resemblance of our patient to his deceased patient.

After the death of the baby, the mother is referred to a perinatologist to plan the next pregnancy, prevention and intrauterine treatment [8].

Limitation

The diagnosis of GALD in our baby was not confirmed genetically as it was not available, and an MRI scan was not performed as the patient's condition was not stable enough to be transferred to an MRI center.

Conclusion

Mild skin darkening in direct hyperbilirubinemia may be due to phototherapy, but a diagnosis of GALD should be considered in infants with cholestasis or liver failure.

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Ethical considerations

This study was approved by the University Ethics Committee with the code: IR.MUBABOLHRI.REC.1402.30.

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Conflict of interest

No interest

Abbreviations

CRP, C-Reactive Protein
CSF, Cerebrospinal Fluid
Hb, Hemoglobin
HCT, Hematocrit
IUGR, Intrauterine Growth Restriction
MRI, Magnetic Resonance Imaging
NICU, Neonatal Intensive Care Unit
NL R, normal range
TORCH, Toxoplasma, Others, Rubella, CMV, Herpes

Laboratory units

g/dl, grams per deciliter
mg/dl, milligrams per deciliter

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ng/ml, nanograms per milliliter
u/l, unit per liter

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