CASE REPORT

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Prevention of Gestational Alloimmune Liver Disease by Intravenous Immunoglobulin Administration in the Second Trimester: A Presentation of Two Cases

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ABSTRACT Gestational alloimmune liver disease (GALD) is characterized by complement-mediated hepatocyte damage by transplacental transmission of maternal antibodies against fetal hepatocyte antigens. GALD's recurrence occurs up to 90% in pregnancies after an affected pregnancy. Intravenous immunoglobulin (IVIG) is a sterile, purified immunoglobulin (IgG) product that is manufactured from pooled human plasma. IVIG typically contains more than 95% unmodified IgG which has intact fragment crystallizable-dependent effector functions in addition to trace amounts of IgA and/or IgM. Indeed, antenatal high-dose IVIG treatment effectively reduces the risk of recurrence. In the present study, we reported two cases with GALD recurrence which was prevented by maternal IVIG administration in the second trimester.

Keywords: Gestational alloimmune liver disease; intravenous immunoglobulin; liver failure; neonatal hemochromatosis

Gestational alloimmune liver disease (GALD) is identified as a member of the maternal-fetal alloimmune diseases. The target of alloantibodies in GALD is fetal liver where specific antigen is believed to be expressed mainly in developing hepatocytes. The attack of alloantibodies causes activation of fetal complement causing a developmental failure of liver parenchyma resulting in replacement of hepatocyte progenitors with mature hepatocytes. The progenitor-induced profibrogenic signals lead to extensive parenchymal fibrosis.[1] Moreover, main phenotypic manifestation of GALD seems to be neonatal liver disease associated with hemosiderosis of various extra-hepatic tissues which is defined as neonatal hemochromatosis (NH).[2] Consistent with the alloimmune mechanism, GALD exhibits high recurrence rates up to 90% in pregnancies that can be prevented by antenatal intravenous immunoglobulin (IVIG) treatment.[1,3-5] In the present study, we reported two cases with GALD recurrence that was prevented by antenatal IVIG treatment in the second trimester.

CASE REPORTS

CASE 1

A 30-year-old woman, gravida 3 para 1 with a history of GALD, applied for prenatal consultation at 24 week of gestation (WG). The index case was uncomplicated until 37 WG. However; at this time, oligohydramnios and fetal growth restriction were

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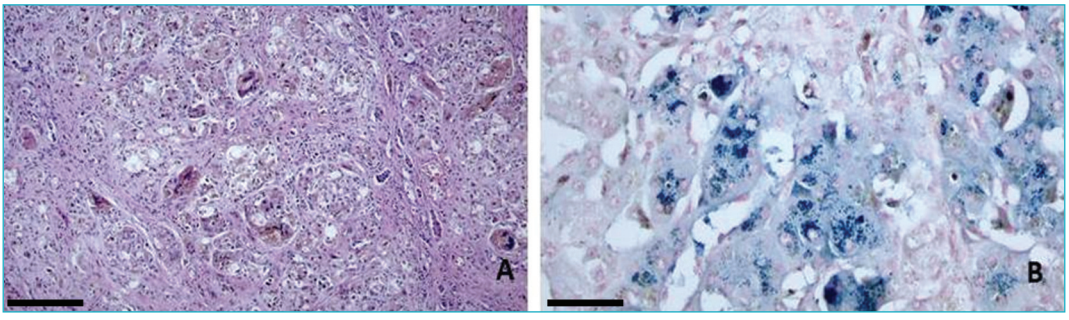

FIGURE 1: The liver histopathology of the first case. A) The microscopic findings included large areas of hepatic necrosis, multinuclear giant hepatocytes, a severe hepatocyte hemosiderosis. The parenchyma consists of fibrosis surrounding pseudorosettes of regenerating hepatocytes and bile accumulation, consistent with fulminant hepatitis and neonatal hemochromatosis (H&E; original magnification x50). B: Prussian blue stain shows multiple intracelluler iron deposits within the hepatocytes (Prussian blue with H&E; magnification x400). Scale bar represents 500 µm.

revealed by an obstetric ultrasound examination. The newborn was delivered through emergency cesarean section. Shortly after birth, acute liver failure occurred in the newborn. At one-month of age, liver transplantation was performed, while his post-transplant course was unremarkable. He is currently 7 years old and healthy. The histopathological examination of the liver revealed large areas of hepatic necrosis, occult inflammatory infiltration, multinuclear giant hepatocytes, and severe hemosiderosis which were consistent with fulminant hepatitis and NH (Figure 1). The diagnosis of GALD was performed by excluding other possible causes of NH. Despite the pregnancy was at an advanced stage, she was treated with IVIG at a dose of 1 $g \cdot kg^{-1}$ weekly from 27 to 36 WG without any complications. A 2,510 g male newborn was delivered by cesarean at the 37 WG. The Apgar scores were 8 and 9 at first and fifth minutes. In early neonatal period, no hypoglycemia, jaundice, ascites occurred; whereas, liver function test results were within normal limits. Currently, he is sixteen months old and healthy without any sign of GALD.

CASE 2

A 29-year-old pregnant, gravida 7 para 5 with a history of GALD was admitted to the hospital for prenatal consultation at the 24 WG. Her first three pregnancies were complicated by fulminant liver failure and neonatal death in the neonatal period. The etiology of liver failures was not investigated. The index case was born at the 39 WG, while the birth weight

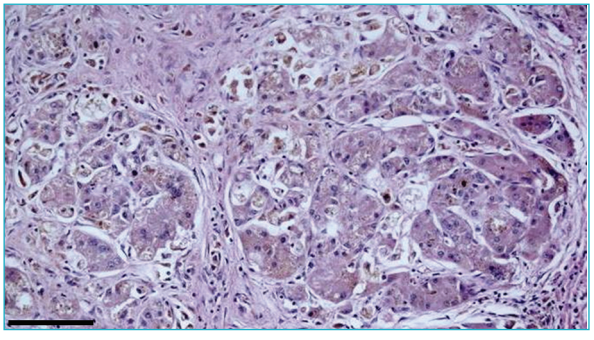

FIGURE 2: The liver histopathology of the second case. The microscopic findings showed severe hepatocyte hemosiderosis in a cirrhotic background (H&E; magnification x400). Scale bar represents 500 µm.

was 3,760 g. Shortly after the birth, she presented with recurrent hypoglycemia. Additionally, the blood tests showed hyperbilirubinemia, hypoalbuminemia, and coagulopathy where the elevated ferritin levels were progressively worsened throughout the first month of life. The work-up for neonatal liver failure such as metabolic disease was negative. Due to worsening of the liver failure, an emergency liver transplantation was performed from the maternal donor, however, she died at the age 22nd month as a result of chronic rejection and liver failure. The performed examination revealed a severe hepatocyte hemosiderosis which was considered to be consistent with fulminant hepatitis and NH (Figure 2). The diagnosis of GALD was conducted by excluding other possible causes of NH. Although antenatal IVIG treatment was recommended in the next pregnancy, the family refused the treatment. The pregnancy was compli-

cated by fetal death at the 32 WG. In her current pregnancy, she received 1 g·kg^{-1} IVIG weekly from 25 to 36 WG without any complications. She underwent a cesarean section with delivery of 3,200 g neonate at the 37 WG, the recorded Apgar scores were 8 and 9 at first and fifth minutes, respectively. Additionally, no sign of hepatic dysfunction was observed in the neonatal period. Her hepatic function was monthly evaluated and normal values were detected within the first 6-month period.

Informed consent forms were obtained from the patients.

DISCUSSION

In this paper, we have reported two cases in which GALD recurrence was prevented by administering maternal IVIG in the second trimester. The principal components of IVIG are the IgG antibodies which compromise approximately 90% of the IVIG preparation. Antibodies are glycoproteins that are synthesized and secreted by plasma cells in response to an antigenic stimulation.[6]

IVIG has been widely used in pregnancy to treat severe alloimmune conditions including neonatal alloimmune thrombocytopenia and a hemolytic disease of the fetus for early-onset severe intrauterine disease.[7] The pathophysiological basis of the use of IVIG in GALD is similar to other alloimmune diseases so that it dilutes the maternal antibodies to fetal liver antigens, while crossing the placenta at a lower rate. Through blocking the placental receptors, IVIG reduces the placental transmission of maternal antibodies to the fetus. Moreover, it antagonizes the fetal fragment crystallizable receptors on macrophages, thereby inhibiting destruction of the antibody-covered fetal cells.[1]

In 2004, antenatal IVIG therapy was demonstrated to prevent the recurrence of GALD in which the IVIG regimen was carried out weekly from the 18 WG to the end of pregnancy.[8] Based on the old protocol, the treatment initiation week was revised to 14 weeks after two women who started treatment 16 and 17 WG experienced stillbirth at 18 to 22 weeks. The current treatment consists of antenatal IVIG (1 g·kg^{-1}) administrations at 14, 16, 18 WG and continued weekly to the end of pregnancy.[1,3-5] It seems to be crucial to continue treatment until at least the 35 WG, for a total of 20 doses; whereas, the recommended dose is 60 g considering the side effects and the required infusion time.[1]

It is important to note that in both of the presented cases, the treatment was initiated later than the recommended gestational week due to late admission to our clinic. Whittington compared a total of 188 high-risk pregnancies with untreated pregnant women treated with antenatal IVIG, whereas the therapy was initiated in 4 cases at 20-29 WG. While the treatment results of 3 cases were favorable, the infant who started antenatal treatment at the 21 WG died while waiting for liver transplantation.

In a prospective multicenter study, 1 in 8 women given antenatal IVIG stopped treatment early after only 2 infusions, her child did not present with any sign of liver disease at birth but the next sibling died of NH because the mother had declined antenatal IVIG treatment. The authors argued that IVIG may only be necessary for a short period of time during which maternal alloimmunization occurs.[9] Although the active transport of liver IgG antibodies from mother to fetus starting from about 12 WG; in our cases, maternal alloimmunization may not have occurred before the start of the treatment.[10] Thus, the antenatal IVIG treatment might have been effective.

The most important limitations of IVIG infusion are considered to be the cost, the side effects, and availability.[10] In fact, there were no IVIG-related side effects in our patients. However, the IVIG therapy has considerable risk of adverse effects including headaches, chills, flushing. IVIG-associated maternal hemolysis, and other cytopenias that have also been noted in the literature.[11-13] In the current literature, a case has been reported in which plasmapheresis was performed during pregnancy as a cost effective alternative to prevent recurrent GALD.[14]

As a result; GALD is now well established as a gestational alloimmune disease and the risk for recurrence in subsequent offspring of an affected woman is very high. However, prevention of recurrent severe

NH by gestational treatment using IVIG has been quite effective. To prevent recurrence of GALD, high-risk pregnancies should be evaluated in terms of antenatal IVIG therapy, even at advanced weeks of pregnancy.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gül Alkan Bülbül, Cem Yaşar Sanhal;* ***Design:*** *Gül Alkan Bülbül, Cem Yaşar Sanhal;* ***Control/Supervision:*** *Cem Yaşar Sanhal;* ***Data Collection and/or Processing:*** *Gül Alkan Bülbül, Emine Kirtiş, Arzu Aras, Hülya Kandemir;* ***Analysis and/or Interpretation:*** *Gül Alkan Bülbül, Özlem Elpek;* ***Literature Review:*** *Gül Alkan Bülbül, Hülya Kandemir;* ***Writing the Article:*** *Gül Alkan Bülbül;* ***Critical Review:*** *Cem Yaşar Sanhal;* ***References and Fundings:*** *Cem Yaşar Sanhal;* ***Materials:*** *Özlem Elpek, Gül Alkan Bülbül.*

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