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Letter to the Editor

Fetal cholelithiasis in a case of beta-thalassemia major

ARTICLE INFO

Keywords:

Beta-thalassemia major
Fetal cholelithiasis
Gallstone
Neonate

ABSTRACT

Fetal cholelithiasis, reported as echogenic material in fetal gallbladder, is an infrequently encountered condition. Association of fetal cholelithiasis with beta-thalassemia is rare. We report incidental detection of cholelithiasis in a fetus during routine antenatal ultrasonography at 39 weeks of gestation. The gallstones persisted beyond the neonatal period, and the infant was later diagnosed as beta-thalassemia major. Both the parents were known cases of beta-thalassemia trait with their earlier two children diagnosed as beta-thalassemia major.

We highlight the importance of awareness for the treating physician about this uncommon complication of beta-thalassemia major, while managing an apparently asymptomatic neonate.

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Sir,

Fetal cholelithiasis, reported as echogenic material in fetal gallbladder in third trimester of pregnancy, is an infrequently encountered condition of uncertain clinical significance.^{1–5} The exact etiology is unknown. Potential maternal risk factors include abruption placentae, increased estrogen levels, dehydration, diabetes, sepsis, leukemoid reaction, and drugs, including ceftriaxone, furosemide, and prostaglandin E₂. Common fetal risk factors include hemolytic anemias presenting in neonatal period, ABO or Rh incompatibility, multiple pregnancy with demise of one fetus, Down syndrome, intra-uterine growth restriction, congenital infections, biliary cholestasis, and idiopathic.^{2–7} Association of chromosomal aberrations, cardiac malformations, and gastroschisis has also been reported.⁶ Unlike spherocytosis, glucose 6-phosphate dehydrogenase deficiency or alpha-thalassemia, beta-thalassemia does not manifest in the neonatal period. We report cholelithiasis in a fetus that was subsequently diagnosed as beta-thalassemia major. Such a case is not reported in literature.

A 29-year-old, third-gravida mother, presented in Obstetric Emergency in labor at 41 weeks' of gestation. Both she and her husband were known cases of beta-thalassemia trait. Both of their earlier two children, diagnosed as beta-thalassemia major, died at young childhood after receiving multiple transfusions. Antenatally, there was no history of any drug

intake, sepsis, leukemoid reaction, dehydration, oligohydramnios, per vaginal leak or bleed, abruption placentae, and diabetes mellitus. Antenatal ultrasound done at 39 weeks' of gestation demonstrated a singleton live fetus with multiple echogenic foci within an enlarged gallbladder, suggestive of fetal cholelithiasis (Fig. 1A). Fetal liver echogenicity was normal, and there was no meconium peritonitis or any other structural abnormality. Mother's own gallbladder was normal. Clinically, the mother had moderate pallor with palpable spleen tip. Her hemoglobin was 7.2 g/dL, total leukocyte count (TLC) was 7200/μL and blood group was B-positive. Peripheral blood smear showed anisocytosis, poikilocytosis, fragmented RBCs and tear drop cells, suggestive of hemolysis.

A baby-girl weighing 3375 g was delivered by cesarean section. There was no jaundice, hepatosplenomegaly or palpable gallbladder. CBC showed hemoglobin of 16.2 g/dL, TLC of 10,200/μL and a platelet count of 2,20,000/μL and no evidence of hemolysis in peripheral blood smear. Reticulocyte count was 2.1%, and direct Coomb's test was negative. Metabolic profile, lipid profile, liver, and renal function tests of the neonate were normal. Blood glucose remained above 45 mg/dL throughout the infant's stay in neonatal unit; ionic calcium was 1.2 mmole/L, serum sodium was 142 meq/L, and serum potassium was 4.2 meq/L. Total serum bilirubin done on day 3 of life was 4.2 mg/dL (indirect 3.8 and direct 0.4 mg/dL). Liver enzymes were normal. Blood urea was 18 mg/dL and serum creatinine was 0.6 mg/dL. Serum

Fig. 1 – (A) Transverse image through the fetal abdomen showing multiple small echogenic foci within the gallbladder. (B) Abdominal ultrasound of the baby showing multiple foci of echogenicity arising from both the walls of gallbladder and sludge within the lumen.

cholesterol, triglyceride, high-density lipoprotein, very high-density lipoprotein, and low-density lipoprotein concentrations were 98.3, 87.4, 20.8, 17.4, and 55.8 mg/dL, respectively. Karyotyping was 46,XX. Screening for congenital infections including Human Immunodeficiency Virus infection, hepatitis B, syphilis, Cytomegalovirus, Toxoplasma, Rubella, and Herpesvirus was negative. Arterial blood gas analysis showed normal pH (7.42), blood lactate and serum ammonia levels were normal, and tandem mass spectrometry for inborn errors of metabolism was negative. Abdominal ultrasonography done at 2 days of life showed multiple foci of echogenicity arising from both the walls of gallbladder and sludge within the lumen suggestive of gallstones (Fig. 1B). Rest of the hepatobiliary system and abdomen was normal. Since the infant was asymptomatic, after consultation with Pediatric Surgery, a decision was made to keep her under follow-up. The infant came to follow-up at 6 months of age with moderate pallor (hemoglobin 6.2 g/dL, microcytic hypochromic anemia) and hepatosplenomegaly (liver 4 cm and spleen 5 cm below costal margins). Peripheral blood smear showed features of hemolysis (anisocytosis, poikilocytosis, normoblasts, pencil cells, fragmented RBCs, and tear drop cells). Hemoglobin electrophoresis showed fetal hemoglobin of 88.4% and HbA2 of 3.2%, suggestive of beta-thalassemia major. Ultrasonography abdomen showed an increase in the size of gallstones. The parents were advised for blood transfusion and the option for bone marrow transplant was discussed. For gallstones, pediatric surgeons advised for cholecystectomy. Considering the poor prognosis of their earlier two children, the parents refused for any further treatment and lost to follow-up.

First case of fetal cholelithiasis was diagnosed in 1928 during autopsy,⁸ and the first prenatal diagnosis was made in 1983.² The incidence of fetal gallbladder anomalies including biliary sludge and gallstones is 0.42%, with slight male preponderance.^{1,9} Fetal gallstones are formed secondary to abnormal production, composition, and transportation of bile in the biliary tract.^{2,10} The major theories proposed are breakdown of placental hematoma with increased indirect bilirubin levels, or increased secretion of cholesterol and

depressed bile acid synthesis caused by the influence of maternal estrogens leading to the formation of pigment stones.^{1,7}

Management of fetal cholelithiasis includes close follow-up, as most of the authors reported spontaneous resolution prior to delivery or postnatally within weeks to months.^{1–5} Most neonates have spontaneous passage of gallstones or resolution with postnatal hydration, though rarely it can persist causing neonatal cholelithiasis, stones in common bile duct, and peritonitis.^{1,10–12} Requirement of cholecystectomy is rarely reported after the development of chronic cholecystitis.¹² Use of ursodeoxycholic acid also has been reported to cause the resolution of gallstones.¹³

It is difficult to ascertain the cause of gallstone in our case, since none of the commonly reported maternal or neonatal risk factors were present. Though the mother had evidence of chronic hemolysis, she did not have any gallstone herself. Also, there was no evidence of hemolysis in the neonate at birth, which could have led to gallstone formation. The cause of persistence and increase in size of gallstones beyond the neonatal period was probably because of the ongoing hemolysis secondary to the disease process of beta-thalassemia major. The long-term consequence of gallstones in our case remained unclear, as we lost the infant in follow-up.

In India, the diagnosis of beta-thalassemia is worrisome for the parents, as the facilities for regular blood transfusion and iron chelation are limited. Bone marrow transplant is costly and beyond the reach of most of them. Addition of an unusual complication, such as fetal cholelithiasis, brings a lot of dismay to the parents, and the treating physician faces difficulty in explanation and prognostication of the condition. Through this case report, we highlight the importance of awareness about this uncommon complication of beta-thalassemia major in an apparently asymptomatic neonate.

Conflicts of interest

The authors have none to declare.

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<http://dx.doi.org/10.1016/j.cegh.2015.07.005>
2213-3984/

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