CASE REPORT

The Icteric Riddle: A Diagnostic Conundrum to Diagnose Maternal Dubin–Johnson Syndrome

Aditya Rajiv Nimbkar[1], Shruti A Panchbudhe[2], Prasad Deshmukh[3], Sumedha S Pathade[4]

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Abstract

Aim: To diagnose a rare congenital liver disorder, Dubin–Johnson Syndrome (DJS), compounded by pregnancy and its several differential diagnoses that impede the progress toward diagnosis.

Background: Icterus, or jaundice, is defined as the yellow discoloration of the skin, more so of the sclera. While it classifies as one of the most common symptoms in medical literature, it gains added significance when it arrives in congruence to pregnancy. And with that added significance comes the increased risk of maternal and fetal morbidities and mortalities.

Case description: Here, we discuss a 19-year-old antenatal patient with refractory hyperbilirubinemia whose etiology eluded our team, until a final shot at it through liver biopsy helped us fetch a surprising diagnosis of DJS.

Conclusion: A nonfatal clinical syndrome with very few comorbidities, pregnancy at worst, worsens the icteric component without producing too many adverse fetomaternal outcomes.

Clinical significance: The aid of a sound algorithm to rule out other more morbid causes of hepatic dysfunction in pregnancy.

Keywords: Autosomal-recessive, Dubin–Johnson Syndrome, Jaundice in pregnancy, Liver disease in pregnancy, Ursodeoxycholic acid.

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Case Description

A 19-year-old female, primigravida with 34 weeks of gestation, was referred to our outpatient department of tertiary care hospital, in view of raised serum bilirubin levels. On further interrogation, the patient revealed the presence of icterus since childhood, and her routine antenatal investigations revealed the presence of hyperbilirubinemia. The patient gave no history of fever, upper abdominal pain, itching over, or altered urine and stool color.

On examination, the patient had icterus but no evidence of jaundice anywhere else, except sclera, as seen in Figure 1. Her vitals were within normal limits, and blood pressure was astutely monitored to be able to diagnose any evidence of pre-eclampsia-induced liver damage. As per abdominal examination, the fetus shows growth corresponding to its gestational age. Routine blood investigations showed total bilirubin level to be 3.7 mg/dL, with direct bilirubin at 3.1 mg/dL, thereby suggesting direct bilirubinemia rather than indirect. Normal platelet counts, liver enzymes, and normal-ranged markers of hemolysis ruled out HELLP syndrome. Yet, to rule out indirect and mixed hyperbilirubinemia, further blood investigations were done, which revealed normal levels of serum lactate dehydrogenase and reticulocytes and negative indirect and direct Coomb's test, thereby ruling out hemolytic causes of hyperbilirubinemia.

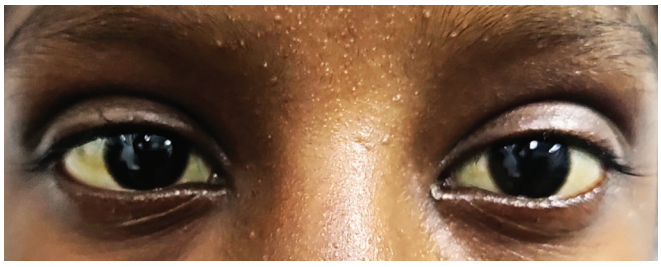

Fig. 1: The icteric sclera

To know the origin of direct bilirubinemia, fasting bile acid levels, serum ammonia, transaminases, and gamma-glutamyl transferase were done, which were normal. Alkaline phosphatase was raised to 118 mg/dL, but that could be attributed to its placental isoenzyme that is physiologically released during pregnancy. Flummoxed regarding the continual inconclusive blood investigations, autoimmune workup was sought with ANA and antimicrosomal antibody levels reporting to be within normal range as well. Viral hepatic markers were negative as well. Urobilinogen was not noted in routine urine microscopic examination either.

Unsure of the diagnosis, gastroenterology and surgical teams' consultation was sought. A hepatobiliary scan was performed, and mild hepatomegaly was visualized without any alteration of its echotexture nor any dilatation of intrahepatic biliary radicles seen. Biweekly monitoring of her liver function tests

[1–4]Department of Obstetrics and Gynaecology, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India

Corresponding Author: Aditya Rajiv Nimbkar, Department of Obstetrics and Gynaecology, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India, Phone: +91 7666842282, e-mail: nimbkaradi17@gmail.com

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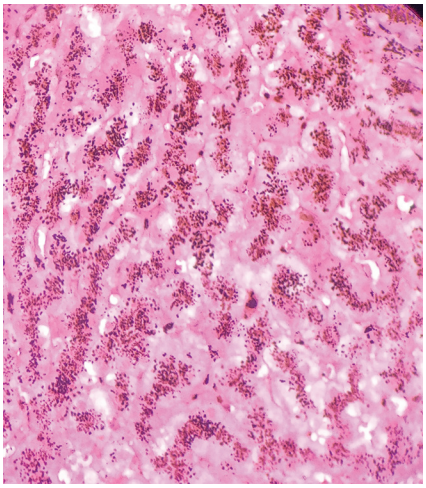

Fig 2: Masson Fontana staining of lipofuscin–melanin pigment in hepatocytes (40× magnification)

was done, and the total bilirubin was consistently in the range of 3.5–4.5 mg/dL with a significant direct component to it. A magnetic resonance cholangiopancreatography (MRCP) scan was advised with gadolinium contrast after delivery of the fetus. The patient was started on ursodeoxycholic acid 300 mg twice-daily supplements until then. But her serum bilirubin levels relentlessly stayed constant at their aforementioned levels.

The patient went into spontaneous labor at 37 weeks of gestation and delivered a male fetus weighing 2.8 kg normally and vaginally. The baby had a healthy outcome and cried immediately at birth. Post delivery, her liver function tests were repeated but the hyperbilirubinemia trend continued. The MRCP, as advised earlier, was undertaken, which showed mild hepatomegaly without any other changes in the hepatobiliary and pancreatic systems.

Finally, as a last resort, a liver biopsy was performed by intervention radiologists under ultrasound guidance and the sample was sent for histopathological examination along with culture and sensitivity examination, including that of Mycobacterium. That was when the case broke open finally. Although the culture examination reported no microbiological growth, the histopathological examination using Masson Fontana staining, as seen in Figure 2, along with black pigmentation of the tissue's lipofuscin–melanin[1] revealed a surprising cause of congenital hyperbilirubinemia, the DJS.

A gastroenterology consultation was sought, and expectant management was advised with regular follow-up to their outpatient department. The patient and the baby had an uneventful postnatal period and were advised genetic testing for ABCC2 mutation at 6 months of infancy.

Discussion

Liver disorders in pregnancy are a segment that can excite as well as worry obstetricians with equal measure.[2] While relatively benign conditions that cause hyperbilirubinemia like hyperemesis gravidarum, autoimmune hepatitis, or intrahepatic cholestasis of pregnancy can be managed conservatively, conditions with aggressive course like infective and fulminant hepatitis or acute fatty liver of pregnancy can require intensive care unit admission and can be rapidly progressive till fatality.

This particular case had a benign course and hence was followed up on an outpatient basis. Ruling out major adversaries like intrahepatic cholestasis[2] with normal-fasting bile acid levels, acute fatty liver in view of stable vitals, and normal serum ammonia that is raised, leading to its classical encephalopathy and viral hepatitis markers being negative, helped us approach the case with a wait-and-watch expectant course until spontaneous labor set in.

Dubin–Johnson syndrome is a rare autosomal-recessive disorder.[3,4] As eventually diagnosed on histopathological examination is a form of congenital hyperbilirubinemia along with Rotor syndrome. The differentiating factor between these two was the black pigmentation of the tissue on microscopic examination and nonvisualization of the enlarged gall bladder in DJS. At the molecular level, DJS is caused due to loss-of-function mutation of multiple drug-resistance protein 2 manufactured from the gene ABCC2 (ATP-binding cassette subfamily-C member) that is located on chromosome 10 and helps in biliary excretion of bilirubin glucuronides, thereby eventuating its deposition in the hepatocytes and blackish discoloration.

Literature has sporadically reported cases of DJS over the years. Most patients are asymptomatic apart from the presence of icterus. It is said to be exacerbated with pregnancy, although these findings have not been consistent enough. Fetal morbidities are not known, unlike in other forms of pregnancy-related hyperbilirubinemia, since conjugated bilirubin does not cross the placental barrier to cause kernicterus in the fetus, while unconjugated does. While DJS patients have history of stillbirths, recurrent spontaneous abortions, and preterm births, our patient had a successful obstetric outcome in her first pregnancy itself.

The management of DJS is largely conservative with regular monitoring of blood parameters. The patient was advised to avoid hormonal bases' contraceptive agents, especially the ones containing estrogen to avoid flaring up of the existing hepatic disorder.

Acknowledgment

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