CASE REPORT

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Severe jaundice due to coexistence of Dubin-Johnson syndrome and hereditary spherocytosis: A case report

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Dubin-Johnson syndrome is a chronic, benign, intermittent jaundice, mostly of conjugated hyperbilirubinemia. The level of bilirubin is not expected to be more than 20 mg/dl in this syndrome. In this article, we report a patient who was evaluated for hyperbilirubinemia and liver function test abnormalities and diagnosed with Dubin-Johnson syndrome coexisting with hereditary spherocytosis. We suggest that other diseases should be investigated if patients with Dubin-Johnson syndrome present with severe hyperbilirubinemia. Dubin-Johnson syndrome accompanied by hemolytic diseases might also have high coproporphyrin levels (as in Rotor's syndrome) than expected in pure Dubin-Johnson syndrome.

Key words: Dubin-Johnson syndrome, hereditary spherocytosis, hyperbilirubinemia, hemolytic disease

Dubin Johnson sendromu ve herediter sferositoz birlikteliğine bağlı ciddi sarılık: Olgu sunumu

Dubin Johnson sendromu kronik, benign, sıklıkla konjuge hiperbilirubineminin gözlendiği sarılıkla karakterize bir hastalıktır. Bilirubin düzeyi 20 mg/dl'yi geçmez. Bu yazıda, karaciğer fonksiyon testleri bozukluğu ve hiperbilirubineminin değerlendirilmesi sırasında tespit edilen Dubin Johnson sendromu ve herediter sferositozlu bir hastayı sunduk. Bu vaka bize ciddi hiperbilirubinemisi olan Dubin Johnson sendromlu hastaların diğer hastalıklar açısından da araştırılması gerektiğini göstermiştir. Dubin Johnson sendromu ile hemolitik hastalıkların birlikteliğinde Dubin Johnson sendromlu bir hastada beklenilen koproporfirin düzeylerinden daha yüksek düzeylerde (Rotor sendromunda olduğu gibi) koproporfirin düzeyleri görebiliriz.

Anahtar kelimeler: Dubin Johnson sendromu, herediter sferositoz, hiperbilirubinemi, hemolitik hastalık

INTRODUCTION

Dubin-Johnson syndrome (DJS) is a chronic, benign, intermittent jaundice, mostly of conjugated hyperbilirubinemia (1). It is characterized by a hereditary conjugated hyperbilirubinemia and a typical dark pigment accumulation in liver parenchymal cells (2). The onset of the disease is in early adulthood. Most patients are asymptomatic and have a normal life span. Occasionally, patients complain of weakness and vague abdominal pain, and hepatosplenomegaly is observed rarely (2,3). The incidence of hyperbilirubinemia is increased with intercurrent illness, oral contraceptives and pregnancy (4).

Hereditary spherocytosis (HS) is the most common hemolytic anemia due to a red cell membrane defect (5). Anemia, jaundice and splenomegaly are the common clinical features of HS. The degree of

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anemia is extremely variable and may be absent, mild, moderate, or severe to the point of threatening life (6). A case of hereditary hemolytic disease (due to glucose-6-phosphate dehydrogenase [G6PD] deficiency) together with DJS was reported in the literature (7). We report herein a patient with severe jaundice, apparently aggravated by pneumonia. In this patient with pneumonia, the jaundice was probably aggravated by the unusual coexistence of HS and DJS.

CASE REPORT

A 47-year-old male was admitted to our hospital with abdominal pain and swelling, cough, sputum, malaise, and jaundice. His medical history was remarkable for the diagnosis of HS, for which he was offered and declined a splenectomy 20 years ago. On physical examination, his vital signs were as follows: body temperature 37.8°C, heart rate 100 bpm, blood pressure 110/70 mmHg, and respiratory rate 18/minutes. He was conscious, cooperative and oriented, with pale conjunctivas and profuse jaundice on sclera and skin. On lung auscultation, inspiratory and expiratory rales were heard on both lung fields. Abdominal examination revealed an enlarged spleen extending into the pelvis and hepatomegaly with borders beginning from the sixth intercostal space and ending 5-6 cm below the arcus costarum. Other physical examination findings were considered to be normal.

The patient's laboratory data were as follows: hemoglobin (Hb) 6.16 g/dl, white blood cell (WBC): 11400/mm^3 (83% neutrophils), platelet (PLT): 207000/mm^3, erythrocyte sedimentation rate (ESR): 10 mm/hour, C-reactive protein (CRP) 11.76 g/L, alkaline phosphatase (ALP) 342 U/L (normal range: 30-120 U/L), gamma-glutamyl transpeptidase (GGT) 188 U/L (normal: 9-64 U/L), aspartate aminotransferase (AST) 487 U/L (normal: 0-40 U/L), alanine aminotransferase (ALT) 519 U/L (normal: 0-40 U/L), lactate dehydrogenase (LDH) 558 U/L (normal range: 125-245 U/L), bilirubin 46.4 mg/dl (normal range: 0.3-1.0 mg/dl), direct bilirubin 16.4 mg/dl (normal range: 0.1-0.3 mg/dl), albumin 3.2 g/dl (normal range: 3.5-5.5 g/dl), globulin 2.2 g/dl (normal range: 2.0-3.0 g/dl), prothrombin time 60%, serum iron 75, transferrin saturation 35%, and ferritin 1123 ng/ml. Direct Coombs test was negative. Reticulocyte count was 6%.

On sputum smear, inflammatory cells and diplococci were seen, and after growing *Streptococcus pneumoniae* from sputum culture, ampicillin/sulbactam therapy (4x1 g) was started.

Marked spherocytosis on peripheral smear (Figure 1a), positive osmotic fragility test and splenomegaly were accepted as confirming the diagnosis of HS. Laboratory investigations for hepatitis A, B, and C markers (including IgM anti-HAV, HBs Ag, IgM anti-HBc, anti-HCV antibodies and HCV-RNA), anti-CMV (cytomegalovirus) IgM, anti-EBV (Epstein-Barr virus) IgM, Parvovirus B19 antibody IgM, anti–HIV (human immunodeficiency virus), HSV (herpes simplex virus) 1-2 PCR (polymerase chain reaction), anti-smooth muscle antibodies, anti-mitochondrial antibodies, anti-liver kidney microsome type 1, and anti-nuclear factor were all negative. Abdominal ultrasonography revealed hepatomegaly (170 mm), splenomegaly (226 mm) and cholelithiasis, with no biliary duct dilatation. Histological findings on liver biopsy revealed normal liver architecture with the diffuse intracytoplasmic presence of a coarsely granular, dark pigment in hepatocytes (Figure 1b) and pigment plugs in Herring channels, which were consistent with Dubin-Johnson's pigment (Figure 1c). Additional iron staining showed intracytoplasmic blue granular iron accumulation in hepatocytes (Figure 1d).

Urinary coproporphyrin level was measured as 420 µg/day (normal: 0-150). Type I coproporphyrin level of 339 µg/day (normal: 0-25) (typical for Dubin-Johnson) and type III coproporphyrin level of 50.7 µg/day (normal: 0-75) strongly supported the diagnosis of HS.

With the proper treatment of pneumonia, laboratory findings improved and were as follows: Hb 8.17 g/dl, WBC: 7910/mm^3 (55% neutrophils), PLT 332000/mm^3, ESR: 16 mm/hour, CRP: 0.64 g/L, ALP: 179 U/L, GGT: 49 U/L, AST: 18 U/L, ALP: 18 U/L, LDH: 129 U/L, bilirubin 7.46 mg/dl, direct bilirubin 6.74 mg/dl, albumin 3.2 g/dl, globulin 2.8 g/dl, and prothrombin time 98%. After the stabilization of her clinical status, splenectomy was offered, but the patient declined the procedure and was discharged in good health.

DISCUSSION

In the present case, DJS and HS coexisted based on clinical and histopathological findings. Meanwhile, secondary iron overload was present, which was thought to result from the hemolysis secondary to HS.

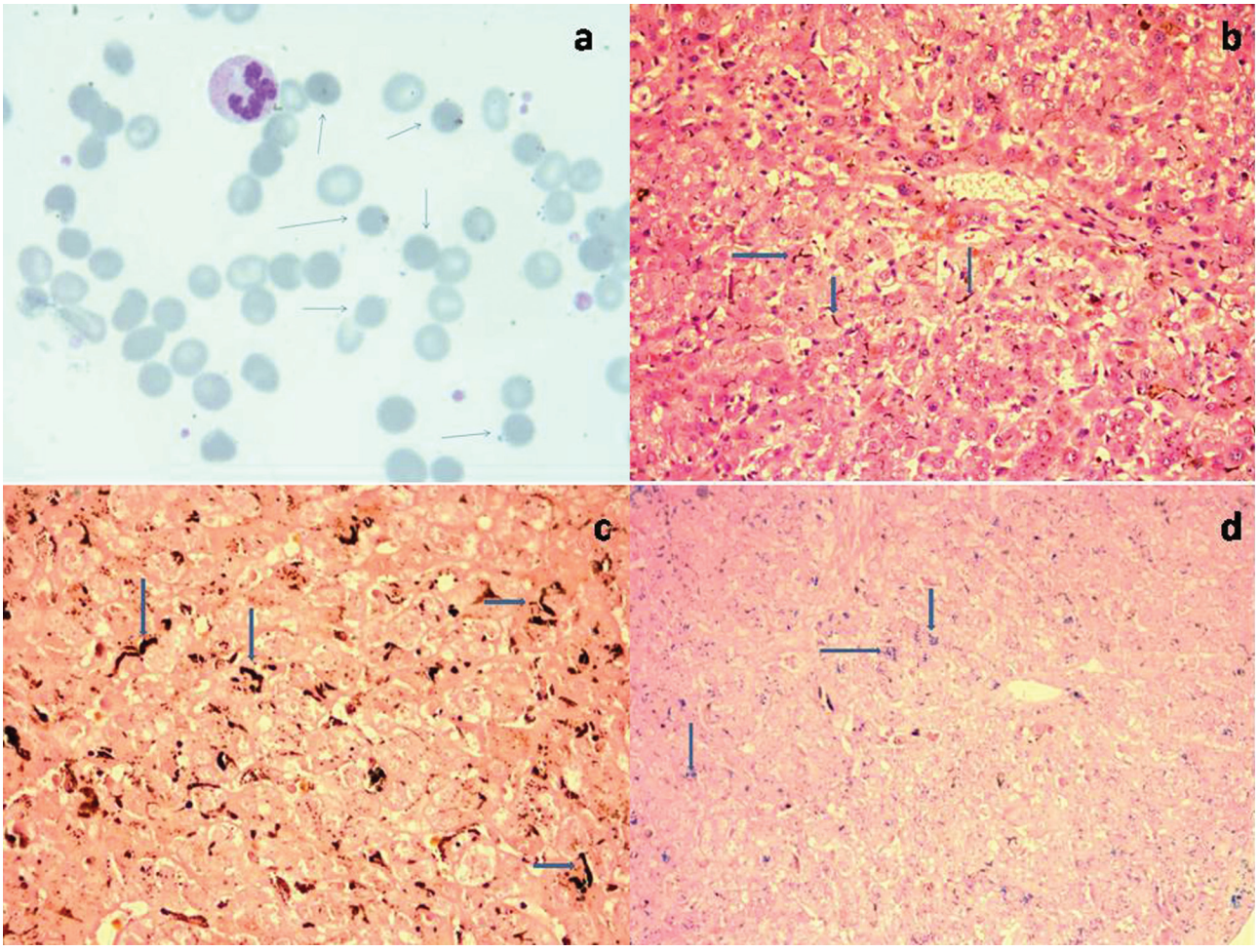

Figure 1. a) Diffuse spherocytes on peripheral smear (arrows) (Giemsa x 100), **b)** diffuse intracytoplasmic pigment accumulation in hepatocytes and pigment plugs in Herring channels (arrows) (HE x 200), **c)** brown-black staining of the pigment with Fontana-Masson dye (arrows) (Fontana-Masson x 200), and **d)** intracytoplasmic blue granular iron accumulation in hepatocytes (iron staining x 100).

The DJS is characterized by a chronic, predominantly conjugated, non-hemolytic hyperbilirubinemia, caused by an impaired hepatobiliary transport system for non-bile salt organic anions in the canalicular membrane of the hepatocyte. Furthermore, liver histology is normal except for the syndrome-characteristic lysosomal accumulation of a black pigment. This pigment was thought to be melanin-like material but this remains controversial (8). Bilirubin levels are usually in the range of 2-5 mg/dl, mostly conjugated bilirubin (3). In our case, a noticeable conjugated hyperbilirubinemia, which is unexpected for DJS, led us to consider an accompanying disorder. Shortening of the life span of red blood cells and hemolysis due to HS together with a decrease in hepatic excretion resulting from DJS are considered to cause striking hyperbilirubinemia.

The DJS is generally regarded as a benign syndrome, in which the hyperbilirubinemia is the sole problem (9). Even though hepatomegaly was present in our case, only a slight hepatic dysfunction was detected. Hepatic iron overload caused by the increase in the amount of iron presented to the liver secondary to HS-related hemolysis was considered to cause this hepatic dysfunction. After the treatment of pneumonia, which was thought to provoke the hemolytic reaction, improvement in hemolysis with simultaneous improvement in hepatic functions supports our hypothesis.

In addition, the urinary coproporphyrin excretion in DJS is abnormal (10).The total urinary coproporphyrin is normal in DJS, but over 80% of it is coproporphyrin I, in contrast to normal subjects, in whom 75% of urinary coproporphyrin is coproporphyrin III (11). The total urinary coproporph-

yrin excretion in Rotor syndrome is increased to 250-500% of normal, and coproporphyrin I constitutes approximately 65% of urinary porphyrins (12). In this presented case, urinary coproporphyrin excretion was increased evidently. Furthermore, this increase is in contrast to the pattern expected in individuals with DJS and was more prominent in coproporphyrin I levels compared to coproporphyrin III levels (80% and 12%, respectively). Pigmented liver tissue in our case favors the diagnosis of DJS rather than Rotor syndrome. As in the case presented by Zamir et al. (7) in which DJS coexisted with hemolysis due to G6PD deficiency, high total coproporphyrin levels suggesting Rotor syndrome were thought to result from HS-related hemolysis. HS-related hemochromatosis may seldom result from iron overload secondary to chronic hemolysis. In the literature, it has been reported that iron accumulation leading to tissue damage persisted even after performing splenectomy. These two conditions were thought to occur independently (13). Massive iron overload may develop in patients with HS and enhanced but ineffective erythropoiesis, which potentially requires increased iron absorption from the gut, and with presumably genetically determined unknown factors to accelerate tissue iron absorption (14). No genetic defect for hemochromatosis was detected in our case. Furthermore, improved hepatic dysfunction after the treatment of pneumonia, which was considered to be responsible for hemolysis, suggests that the iron accumulation in our case resulted from hepatic iron accumulation secondary to hemolysis. However, it should be kept in mind that iron absorption from the gastrointestinal tract is enhanced in this group of patients as a result of hemolysis and secondary erythropoiesis in the bone marrow. Thus, in spite of the treatments targeted to eliminate hemolysis, iron overload and related liver damage may not be prevented in the long-term. Cholelithiasis is another liver disorder related to HS (15). Risk is increased in individuals with conjugation defect. Consistent with the literature, our patient also had multiple gallstones.

In conclusion, to the best of our knowledge, this is the first case in the literature in which DJS and HS were reported together. It should be remembered that total coproporphyrin levels may be higher than expected in DJS coexisting with hemolytic disease. In patients whose biopsy findings support the diagnosis of DJS but total coproporphyrin levels are high, consistent with Rotor syndrome, a hemolytic disease may accompany DJS, and thus a hemolytic process should be investigated in these cases. As DJS is a benign entity, in case of accompanying liver function anomalies during follow-up, a second liver disease should be sought. It should be noted that, although liver function abnormalities may improve by preventing hemolysis (with splenectomy), iron accumulation may persist in other tissues.

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