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Case report

Intestinal metaplasia of gallbladder diagnosed after laparoscopic cholecystectomy in patient with Dubin-Johnson syndrome; Does hyperbilirubinemia protect against gallbladder cancer development?

Dubin-Johnson sendromlu bir olguda laparoskopik kolesistektomi sonrası saptanan safra kesesi inestinal metaplazisi: Hiperbilirubineminin safra kesesi kanseri gelişimine karşı koruyucu etkisi olabilir mi?

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ABSTRACT

This case report describes the incidental diagnosis of Dubin–Johnson syndrome (DJS), a rare autosomal recessive disorder characterized by impaired hepatic bilirubin excretion and the hallmark appearance of a grossly black liver, in a 34-year-old female who underwent laparoscopic cholecystectomy for symptomatic cholelithiasis.

The patient presented with right upper quadrant abdominal pain and mild hyperbilirubinemia. Intraoperatively, the liver was noted to have a strikingly dark pigmentation, prompting a biopsy. Histopathological analysis confirmed the diagnosis of DJS. Additionally, examination of the resected gallbladder revealed focal intestinal metaplasia - an established premalignant lesion associated with an increased risk of gallbladder carcinoma.

This report underscores the rare coexistence of DJS and gallstone disease and confirms that the presence of DJS does not complicate laparoscopic cholecystectomy or predispose to postoperative cholestasis. To our knowledge, this is the first documented case of intestinal metaplasia of the gallbladder in a patient with DJS. These findings highlight the importance of routine histopathological evaluation of cholecystectomy specimens, even in cases where DJS is discovered incidentally, to facilitate early detection of potential premalignant changes.

Keywords: Dubin-Johnson syndrome; intestinal metaplasia; gallbladder cancer; laparoscopic cholecystectomy; bilirubin cytoprotection.

ÖZET

Bu yazıda, semptomatik kolelitiazis nedeniyle laparoskopik kolesistektomi uygulanan 34 yaşındaki bir kadında, nadir görülen ve otozomal resesif kalıtım gösteren Dubin–Johnson sendromu'nun (DJS) rastlantısal tanısı anlatılmaktadır. DJS, hepatik bilirubin atılımında bozulma ve karakteristik olarak belirgin siyah renkli karaciğer görünümü ile tanımlanan bir hastalıktır.

Hasta, sağ üst kadranda karın ağrısı ve hafif hiperbilirubinemi ile başvurmuştur. Operasyon sırasında karaciğerin belirgin koyu pigmentasyonu fark edilmiş ve bu durum biyopsi yapılmasına neden olmuştur. Histopatolojik inceleme sonucunda DJS tanısı doğrulanmıştır. Ek olarak, çıkarılan safra kesesinin incelenmesinde odak intestinal metaplazi saptanmıştır; bu lezyon, safra kesesi karsinomu gelişme riski ile ilişkilendirilen bilinen premalign bir değişikliktir.

Bu olgu, DJS ile safra taşı hastalığının nadir birlikteliğini vurgulamakta ve DJS varlığının laparoskopik kolesistektomiye engel oluşturmadığını ya da postoperatif kolestaza yatkınlık yaratmadığını ortaya koymaktadır. Bildiğimiz kadarıyla, DJS tanısı almış bir hastada safra kesesi intestinal metaplazisinin rapor edildiği ilk olgudur. Bu bulgular, DJS tanısı rastlantısal olarak konmuş olsa bile, olası premalign değişikliklerin erken saptanabilmesi açısından kolesistektomi materyallerinin rutin histopatolojik değerlendirilmesinin önemini ortaya koymaktadır.

Anahtar kelimeler: Dubin-Johnson sendromu; intestinal metaplazi; safra kesesi kanseri; laparoskopik kolesistektomi; bilirubin sitoproteksiyonu.

INTRODUCTION

Dubin Johnson syndrome (DJS) is a well-known autosomal recessive disorder of reduced hepatic bilirubin clearance and defective conjugated bilirubin excretion into bile. It presents with mild conjugated hyperbilirubinemia accompanied by normal liver function tests with most patients being asymptomatic except for occasional abdominal pain. The largely unique “black liver” is characteristic of this disorder (1, 2). It consists of the accumulation of dark granular pigment in centrilobular hepatocytes of a liver with otherwise normal parenchymal structure (1,2). Although hyperbilirubinemia has been presumed to prevent the process of atherogenesis and cancerogenesis mainly by decreasing oxidative stress, several papers have proven the inconsistency of this theory, and that no association exists between serum total bilirubin levels and risk of overall cancer (3). In this article, the coexistence of DJS and intestinal metaplasia of gallbladder, a condition associated with increased risk of Gallbladder carcinoma, is presented in a patient who underwent laparoscopic cholecystectomy and was incidentally diagnosed with DJS on gross appearance during the operation.

CASE

A 34-year-old female presented to the emergency department of our hospital with a four-day history of right upper quadrant abdominal pain. On physical examination, Murphy's sign was negative and there was no abdominal tenderness and rebound. Abdominal ultrasonography and computerized tomography showed minimal thickening of the gallbladder wall with numerous intraluminal stones suggestive of chronic calculous cholecystitis (Figure 1). Liver panel results were normal, with the exception of mildly elevated total bilirubin (1.6 mg/dL) and direct bilirubin (1 mg/dL). Preoperative results of the liver function tests were as follows: Aspartate aminotransferase (AST) 25 U/L; alanine transaminase (ALT) 32 U/L; total bilirubin 1.2 mg/dL; and direct bilirubin 0.6 mg/dL. An unexpected finding of a "black liver" was noted during elective laparoscopic cholecystectomy, leading to the decision to perform a liver biopsy (Figure 2).

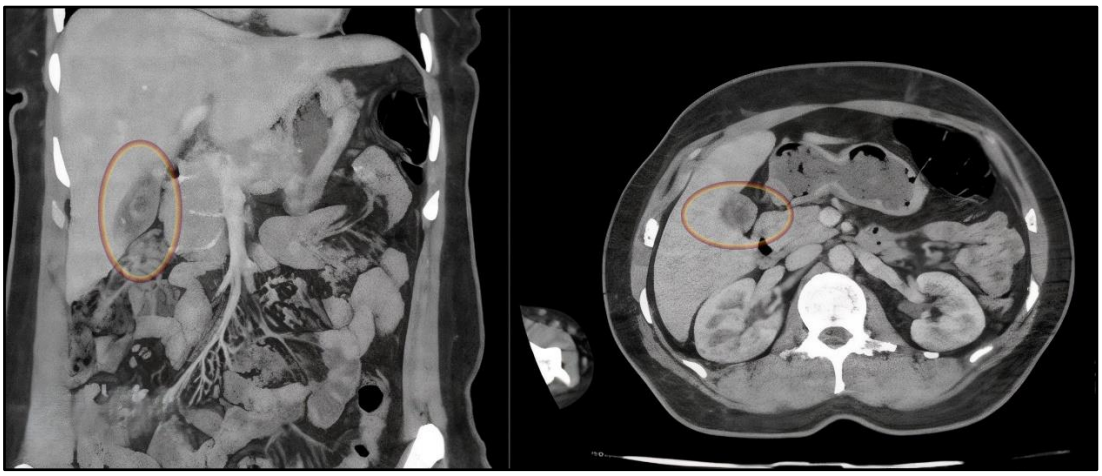

Figure 1: Computed tomography performed upon the patient's arrival in the Emergency Department for acute abdominal pain and discomfort revealed minimal gallbladder wall thickening and luminal gallstones.

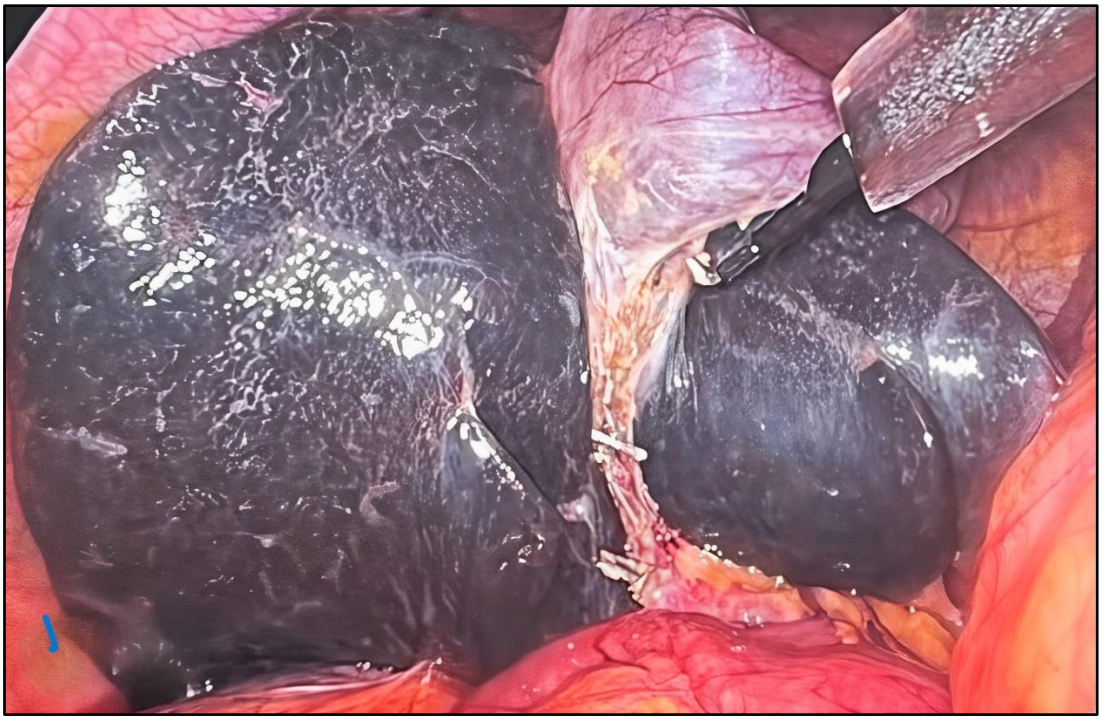

Figure 2: Black liver, considered pathognomonic in Dubin-Johnson syndrome, as discovered incidentally during routine laparoscopic cholecystectomy.

The cholecystectomy was completed successfully without any intraoperative or postoperative complications, and the patient was discharged the following day in stable condition. Liver biopsy specimens stained with Periodic Acid-Schiff combined with Diastase (PAS-D) revealed coarse pigment granules in the cytoplasm of centrizonal hepatocytes, while no signs of hemosiderin or ferritin were noted in Prussian blue (1) and Rhodenin stained specimens (Figure 3). Focal intestinal metaplasia and chronic cholecystitis were described in the final pathology report (Figure 4, 5). A repeat liver panel performed six months after surgery showed a similar mildly bilirubin elevation, with total bilirubin 1.6 mg/dL and direct bilirubin 1.2 mg/dL.

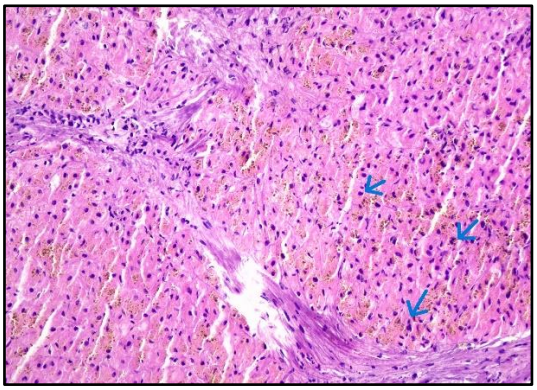

Figure 3: Liver biopsy revealed the accumulation of dark, coarsely granular, melanin-like pigment within centrilobular hepatocytes (arrows), in an otherwise histologically normal liver.

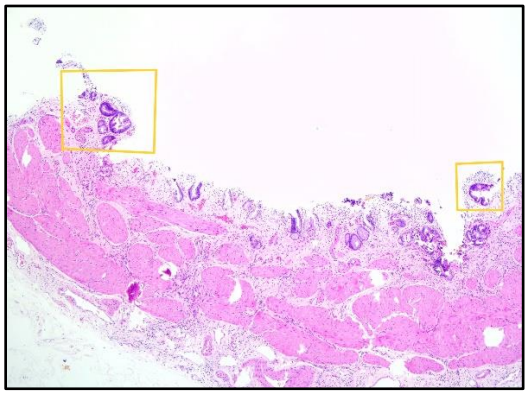

Figure 4: Intestinal metaplasia of the gallbladder mucosa after cholecystectomy.

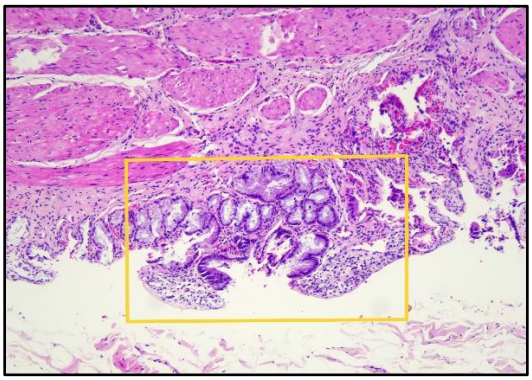

Figure 5: Pseudopyloric intestinal metaplasia as seen on microscopic evaluation of gallbladder specimen.

DISCUSSION

DJS is a rare genetic disease with persistent non-hemolytic hyperbilirubinemia associated with lipochrome-like pigment in liver cells. It was first described in 1954, with the emphasis that all patients with this condition may have the same life longevity as the rest of the population. The prevalence of the disease is estimated to be less than one case per 100,000 individuals globally. It is said to occur equally among both sexes and all races, being more common among Iranian Jews (4). The commonest clinical findings are abdominal pain, fatigue, dark urine and slight hepatomegaly. The coexistence of DJS and cholelithiasis incidence is 10 percent; however, the role of DJS with cholelithiasis remains unclear. There are few cases of "black liver" seen during laparoscopic cholecystectomy, which causes great psychological pressure on the surgeon. Although Dubin-Johnson syndrome is benign and does not require treatment in adults, its diagnosis is essential for distinguishing it from other potentially harmful hepatobiliary disorders. Therefore, a biopsy of liver tissue is always required for diagnosis (5,6).

Persistent cholestasis after cholecystectomy has been reported in some cases, however, many other reports defending that DJS does not increase the risk of cholestasis are present. Since we found that bilirubin values before and after cholecystectomy were similar, we suggest that DJS does not increase the risk of cholestasis in adults.

Gallstones are associated with a variety of epithelial pathology such as hyperplasia, metaplasia and dysplasia which may be precursor lesions of gallbladder cancer. Glandular metaplastic changes in the gallbladder are common, and there are three types of metaplasia of the gallbladder known as intestinal, gastric, and squamous. Intestinal metaplasia is found in 0.9 % to 9.8 % of cholecystectomy specimens, and is known to be associated with an increased risk of gallbladder carcinoma (7,8). Although Gallbladder cancer diagnosed pathologically as differentiated adenocarcinoma has been reported in a 44-year-old man patient suffering from DJS from Japan, intestinal metaplasia of gallbladder after laparoscopic cholecystectomy of a patient with DJS has not been yet reported (9).

Due to its potent antioxidant properties, mild or moderately elevated serum bilirubin has been long believed to provide an endogenous antioxidant and protective effect on carcinogenesis (10,11). Bilirubin typically exhibits anticarcinogenic effects, even at high-normal levels, but can turn protumorigenic under certain conditions. A 2024 study found that exceeding a specific serum threshold diminishes bilirubin's antioxidant capacity, potentially inducing oxidative stress and promoting cancer (12). Other research has also shown bilirubin's tumor-promoting role in liver and lung cancers (13,14). These findings highlight a complex, non-linear relationship between bilirubin levels and cancer risk, where both low and excessively high levels may be detrimental (15). Further research is crucial to fully elucidate bilirubin's dual effects, particularly its pro-oncogenic mechanisms, to ascertain its overall protective or detrimental potential in cancer development.

Conclusion

Although the role of DJS in cholelithiasis remains elusive and unclear, coexistence of DJS and cholecystolithiasis keeps being a rare entity. In cases of symptomatic cholelithiasis, encountering a ‘black liver’ during the operation increases the suspicion of DJS and may frighten the surgeon. It is worth to emphasize that Cholecystectomy is a safe procedure that can be performed in patients with DJS without any preclusions, and that it is appropriate for preventing pre-cancerous lesions of the gallbladder from being overlooked.

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Ethical consideration

Written informed consent was obtained from the patient for publication of this case report and any accompanying images, and was approved by the Ethics committee of Cam ve Sakura Sehir Hastanesi in 21/07/2025 under the number KAEK/16.07.2025.241

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