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Title: Self limiting postoperative hyperbilirubinemia after hepatectomy in a patient of Intrahepatic cholangiocarcinoma (ICC) with Dubin Johnson Syndrome (DJS): A case report

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**Short Running Title:** Case of Hepatectomy in a patient of ICC with DJS

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TITLE: Self limiting postoperative hyperbilirubinemia after hepatectomy in a patient of Intrahepatic cholangiocarcinoma (ICC) with Dubin Johnson Syndrome (DJS): A case report

ABSTRACT

Introduction: Dubin Johnson Syndrome (DJS) is a benign disease of bilirubin metabolism, which causes only jaundice since birth, but there are no other symptoms or signs. DJS is so rare that its exact incidence in Indian population is not known. Incidence of Intrahepatic Cholangiocarcinoma (ICC) is around 3.3%. Occurrence of DJS simultaneous with hepatobiliary malignancies has been reported 4 times previously, predominantly in the Japanese population. There are no reports of such cases from Indian population. Also, in the reported cases the functional reserves of Liver were complicated by presence of pre-existing cirrhosis of Liver. There is no data suggesting the influence of concomitant DJS in a patient with liver cancers.

Case Report: We present a case of 63 year old INDIAN gentleman who was diagnosed with DJS in early thirties and on routine health checkup was found to have Space occupying lesion in Liver. It turned out to be Intra hepatic cholangiocarcinoma on further workup. We state our experience in postoperative management, hyperbilirubinemia as well as further management of disease.

Conclusion: Although it is not possible to predict the exact dynamics of DJS over ICC or vice versa, the outcomes of hepatectomy in such scenario are benign, self limiting and do not require any specific treatment.

Keywords: Dubin Johnson Syndrome, Intrahepatic Cholangiocarcinoma, Hepatectomy, Postoperative hyperbilirubinemia
INTRODUCTION

Dubin Johnson Syndrome is a rare disorder of the bile transport causing mild conjugated hyperbilirubinemia, first described in 1954 as a benign and familial jaundice characterized by the deposition of characteristic black pigment in liver cells. [1] It is a genetically determined pathology of autosomal recessive inheritance.

Intrahepatic cholangiocarcinoma (ICC) is the second most common form of primary hepatic tumor accounting for 3.3% of all such cancers [2]. Etiology is varied and includes many rare disorders [3-11]. Five year survival after operative resection ranges from 25 to 35% [12].

Patients of intrahepatic cholangiocarcinoma with Jaundice usually have advanced locoregional disease and hence have a negative impact on the prognosis [13]. There is one previously reported case of concurrent occurrence of ICC in a patient with DJS from Czech population. So it is difficult to assess influence of mild conjugated hyperbilirubinemia over the outcome of surgery or the disease overall, in presence of such dual pathology.

CASE REPORT

A sixty three year old INDIAN gentleman, who had jaundice all his life and who was diagnosed with Dubin Johnson Syndrome in his early thirties, presented with an incidental lesion in Liver. He was asymptomatic at presentation. He is an occasional alcoholic, nonsmoker with no history suggestive of risk of acquiring hepatitis B or C. He had no medical or surgical co morbidities. On examination he was icteric, but there were no other signs of liver cell failure. Liver was not palpable and no ascites. On an USG examination of abdomen, there was a lesion in the segment V and VI of liver, with features suggestive of neoplastic etiology. A PET CT scan of whole body showed, 7.5 x 5.5 x 4.0 cm lesion with increased FDG uptake (Figure 1 and 2), in Segment IVB and V (SUV max 8.9). Lesion was closely abutting gall bladder.
medially. The blood investigations performed were negative for HIV, HbsAg, HCV. Liver function was normal except for Conjugated Hyperbilirubinemia (Total = 6.5, Direct = 4.5). Rest of his biochemical workup was within normal limits.

In view of a resectable lesion, non Cirrhotic Liver, Child Pugh Group A and MELD score 13, a decision of wide resection of Liver lesion was made. Intra-operative findings were that of no ascites or peritoneal/mesenteric deposits, 8 x 6 x 5 cm hard mass was present in the segment V and VI. There were 2 nodules adjacent to the primary. Liver was resected with a 2-cm margin. Cholecystectomy was done. Post operative course was essentially uneventful. There were no early or late complications. On 3rd Post operative day Bilirubin was 3.8 with direct component of 2.2, which gradually further decreased. (One month post resection T=2.8, D=2.). He was discharged on 4th post operative day. Histopathological analysis showed Poorly differentiated Intrahepatic Cholangiocarcinoma, with Lymphovascular Invasion. All resection margins were free. No nodal disease. GB was uninvolved. (T2bN0M0). He has been on Adjuvant Chemotherapy - single agent Gemcitabine, which was in accordance with the current NCCN guidelines. After 2.5 months of surgery, he is asymptomatic and clinically stable, and is tolerating chemotherapy well.

**DISCUSSION**

Dubin Johnson Syndrome (DJS) is a rare disorder of the bile transport causing mild conjugated hyperbilirubinemia, a benign disorder requiring no treatment. It is a genetically determined pathology of autosomal recessive inheritance, thus favored by consanguineous marriages. The jaundice is stable most of the life except for exacerbations secondary to fatigue, emotional disturbances, physical exercise or infections, often followed by discrete hepatomegaly and choluria [14, 15]. Dubin-Johnson syndrome has been described in all nationalities, ethnic backgrounds, and races. The highest recognized prevalence of the disease (1 case per 1300 population) is in Iranian Jews and is clustered in the same families [16]. The exact incidence of DJS in India is not known. ICC is the second most common primary liver malignancy with a worldwide increase in incidence [17]. Surgical excision has been shown to be associated with increased survival in appropriately selected patients [18]. Alike most solid malignancies aim of
intervention for ICC is R0 resection ensuring the greatest chance of long-term recurrence free and overall survival. Also contributing to the survival are nodal disease and intrahepatic metastases. It has been shown that only surgical excision cannot prolong survival when disease has spread to LNs as well as other parts of liver. Yet, surgery can still provide fair chance of survival if there are no intrahepatic metastases but nodal disease is present [19].

Our patient was diagnosed with DJS in young age and had jaundice as the only symptom, with no interference in his daily activities. He was incidentally found to have a neoplastic lesion with no distant spread, as evident by PET CT scan. It has been found, that the patients with intrahepatic cholangiocarcinoma presenting or developing with jaundice, die within one year of diagnosis and are not the candidates for curative resection. The reason for such a clinical situation is one of the reasons viz., coexistence of tumor invading hepatic artery or portal vein, bilobar involvement of Liver, extensive lymph node involvement or distant metastasis [13]. Only 30-45% of patients are diagnosed before a distant metastasis or jaundice develops [13,20]. In our case, presence of jaundice in this patient of DJS with Liver neoplasm could not be granted the marker of poor prognosis, indirect marker of inoperability or unresectibility. On the contrary, our patient underwent a health checkup on his own, which probably gave a chance of finding this tumor before it could advance locally or metastatize.

Based on the results of PET CT, he was offered an attempt at curative resection. Also, in view of a poorly differentiated tumor and presence of Lymphovascular emboli, we decided to offer him adjuvant Gemcitabine based chemotherapy. There are currently only 4 cases reported in the International literature, of patients suffering from DJS and classic hepatocellular carcinoma [21-24] and one patient reported with DJS and intrahepatic cholangiocarcinoma [25]. None of them are from Indian population. In all cases reported, patient had undergone a massive liver resection. Amongst the cases, Ueno et al [23] and Shikada Y et al [24] reported a post operative hyperbilirubinemia following liver resection. Ueno et al [26], in 1998 reported difficulty in managing the post operative hyperbilirubinemia, requiring the usage of hemopurification, although the specific role of its usage has not been determined. But in 2004, Shikada Y et al [24] reported that there was no requirement
of such technique and bilirubin levels settled gradually. Similar experience was reported by Gamboa C et al [25] after liver resection for ICC. No other significant difference in the context of management of ICC was reported. We report similar experience with post operative hyperbilirubinemia without any specific therapy.

CONCLUSION

DJS and intrahepatic cholangiocarcinoma are diseases of low incidence, and a combination of these two is extremely rare. The pre-operative hyperbilirubinemia in ICC might not be considered a marker for poor prognosis in presence of DJS. Post operative hyperbilirubinemia, appears to be a self limiting problem, but may depend upon preoperative liver reserves and amount of liver resected and/or functional reserve of the remaining liver.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

AUTHOR’S CONTRIBUTIONS

Nagarkar RV –

- Group1 - Conception and design, Interpretation of data
- Group 2 - Critical revision of the article
- Group 3 - Final approval of the version to be published

Roy S

- Group1 - Analysis and interpretation of data
- Group 2 - Critical revision of the article
- Group 3 - Final approval of the version to be published

Tondare AA

- Group1 - Conception and design, Acquisition of data, Analysis and interpretation of data
- Group 2 - Drafting the article, Critical revision of the article
- Group 3 - Final approval of the version to be published

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REFERENCES


TABLES

NIL

FIGURE LEGENDS

Figure 1: CT scan and PET CT image of abdomen in axial view showing the lesion in Liver.

Figure 2: PET CT image of abdomen in coronal section showing the high FDG uptake in the lesion.

FIGURES
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Figure 2: PET CT image of abdomen in coronal section showing the high FDG uptake in the lesion.