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Case Report

Dubin-Johnson syndrome with multiple liver cavernous hemangiomas: report of a familial case

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Abstract: Dubin-Johnson syndrome (DJS) is a rare autosomal recessive inheritance disorder of bilirubin metabolism. Herein we reported a complicated but interesting case which is readily resulted in misdiagnosis or an indefinite diagnosis, and this is the first reported familial case of DJS with multiple liver cavernous hemangiomas. A 49-year-old man was referred to our hospital for jaundice and multiple low-density liver masses. Extensive laboratory investigations showed conjugated hyperbilirubinaemia and positive urine bilirubin. Microscopically, lesions were composed of blood-filled vascular channels of various sizes lined by a single layer of flat endothelial cells supported by fibrous tissue. Coarse brown granules presented in the hepatocytes of the liver lobules locating beside the tumor, particularly in the centrilobular hepatocytes, and the granules showed blue-green with Schmorl's reaction lipofuscin staining. Interestingly, one of the patient's six siblings (female) shared the same condition with him. The relationship between DJS and hemangiomas remains unclear, and it might be contributed to some hereditary factors, or probably occurred simultaneously by chance. It was certified that the true reason for the long-term unclear jaundice was DJS, which was presumed clinically to be caused by bile excretion obstacles associated with the hemangiomas. Liver biopsy and histochemical stain may be helpful to identify the reason of jaundice and avoid misdiagnosis or an indefinite diagnosis.

Keywords: Dubin-Johnson syndrome, cavernous hemangiomas, hyperbilirubinemia, jaundice

Introduction

Dubin-Johnson syndrome (DJS) is a rare autosomal recessive disorder that causes conjugated hyperbilirubinemia without elevation of liver enzymes alanine aminotransferase (ALT) and aspartate transferase (AST). This condition is associated with a defect in the ability of hepatocytes to secrete conjugated bilirubin into the bile. It is usually asymptomatic other than continuing or intermittent recurrent episodes of mild jaundice. Oral cholecystography fails to visualize the gallbladder in patient with the syndrome and biopsy is almost always obtained incidental to a surgical procedure in which the mahogany-colored liver can be observed. Unlike DJS, liver cavernous hemangioma is the most common primary liver tumor. Its incidence in the general population ranges from 0.4-20% [1]. These tumors are frequently asymptomatic and incidentally discovered at imaging, surgery or autopsy. The natural history of liver hemangioma is not completely understood and probably congenital in origin, and hereditary factors may play a role in the pathogenesis of some familial forms of these tumors. But there is no literature on the relationship between these two disorders. A familial case of DJS with multiple liver cavernous hemangiomas is reported here and the possible pathological mechanism, diagnosis and treatment are discussed.

Case presentation

A 49-year-old male was presented with jaundice and yellow urine since childhood and abdominal discomfort and fatigue for 6 months. Liver multiple hemangiomas were found by routine health examination 3 years ago and the maximum one was 1.5 cm. Other original test results are not available. At the time he was not advised any therapy due to no symptom. The

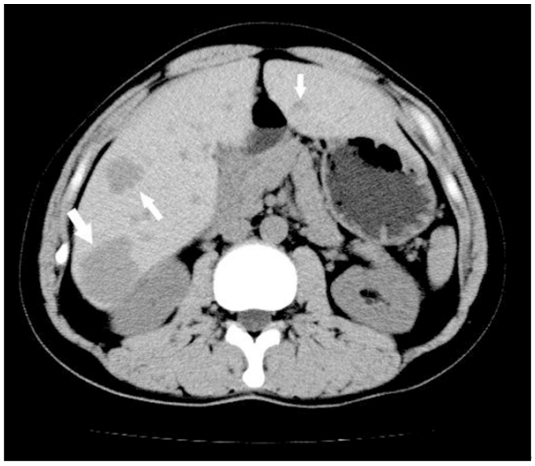

Figure 1. Upper abdominal CT demonstrated multiple hypodense liver masses (white arrow), and dynamic and delayed contrast CT showed a typical enhancing pattern.

ultrasound showed that the maximum hemangioma has grown larger to 6.0 cm before the current hospitalization. Then the operation was advised in our hospital. Physical examination suggested no abnormal findings except for yellow skin and icteric sclera. The abdominal ultrasonography and computerized tomography (CT) indicated multiple liver hemangiomas, however, the size of liver remained normal (**Figure 1**). Laboratory tests before and after the operation were shown in **Table 1**. The clinical diagnosis was hepatic hemangiomas merged with jaundice. The patient underwent minor hepatectomy, during which it was detected that the surface and section of normal-sized liver was black mahogany. Palpable hemangioma measuring 6 cm × 6 cm × 6 cm was observed at Segment VI of right liver, and several other palpable hemangiomas with the maximum diameter of 2 cm were found on the surface of left liver. Microscopically, lesions were typically composed of blood-filled vascular channels of various sizes lined by a single layer of flat endothelial cells supported by fibrous tissue. The structure of the liver lobules locating beside the tumor was normal, but coarse brown granules presented in the hepatocytes, particularly in the central area (**Figure 2A**). The granules showed blue-green with Schmorl's reaction lipofuscin staining (**Figure 2B**), but were negative for Hall's bilirubin stain and Perl's Prussian blue iron staining and Masson-Fontana staining. The final diagnosis was multiple cavernous hemangiomas combined with DJS. Three months after operation, the patient has shown continuing mild jaundice. Interestingly, one of his six siblings (female) has also shown jaundice since her childhood, and multiple low-density masses have been found in the liver indicating cavernous hemangiomas by ultrasonography and CT as well. Due to no evident symptom and the relatively small masses, there is no need for operation and other treatment. Their parents were not consanguineous and found in good health.

Discussion

DJS is also known as congenital nonhemolytic jaundice conjugated with hyperbilirubinemia, which is a rare disorder of bilirubin metabolism and autosomal recessive inheritance. It was first reported by Dubin and Johnson in 1954 [2], and correlated with multidrug resistance-associated protein 2 (MRP2) [3, 4]. The case reported here sharing the same disease with one of the siblings illustrated the character of autosomal recessive inheritance. Generally there is no significant symptom or objective sign, except for the continuing or intermittent recurrent episodes of mild jaundice. Therefore, there is no need for hospitalization. But since the symptom and objective sign are not specific, sometimes it is easily misdiagnosed as other diseases, such as acute or chronic hepatitis and biliary cirrhosis. In this case, the patient with jaundice has not sought for medical advice for about three decades until the multiple hemangiomas gradually increased in recent years. In addition to high direct bilirubin (DBIL) (more than quintuple of normal) and urine bilirubin, all other laboratory test results were normal, including AST, ALT, alkaline phosphatase (ALP), and gamma-glutamyltransferase (γ-GT). And serum test to hepatitis A, B, C, D and E were all negative. The abdominal ultrasonography and CT showed exclusively multiple liver hemangiomas. So in addition to the clear preoperative diagnosis of multiple hemangiomas, the patient was also complicated with jaundice which was presumed clinically to be caused by bile excretion obstacles associated with the hemangiomas. Liver biopsy and histochemical stain have indicated that the true reason for jaundice is DJS. The complexity and atypism of this case and the lack of awareness of this disease had resulted in a long-term indefinite diagnosis. Therefore, the diagnosis of this syndrome was performed by using histopathology of liver biop-

Table 1. Different parameters of liver functions before and after the operation

	TBIL (umol/L)	DBIL (umol/L)	IBIL (umol/L)	ALT (IU/L)	AST (IU/L)
3 Day before surgery	45.7	29.6	16.1	20	12
1 Day before surgery	35.0	25.9	9.1	20	11
1 Day after surgery	84.6	59.9	24.7	460	206
2 Day after surgery	100.6	94.6	6.0	422	134
3 Day after surgery	158.2	N/A	N/A	258	55
4 Day after surgery	139.8	107.4	32.4	190	38
5 Day after surgery	113.2	93.2	20.0	90	19

Abbreviations: TBIL: total bilirubin; DBIL: direct bilirubin; IBIL: indirect bilirubin; ALT: alanine aminotransferase; AST: aspartate transferase.

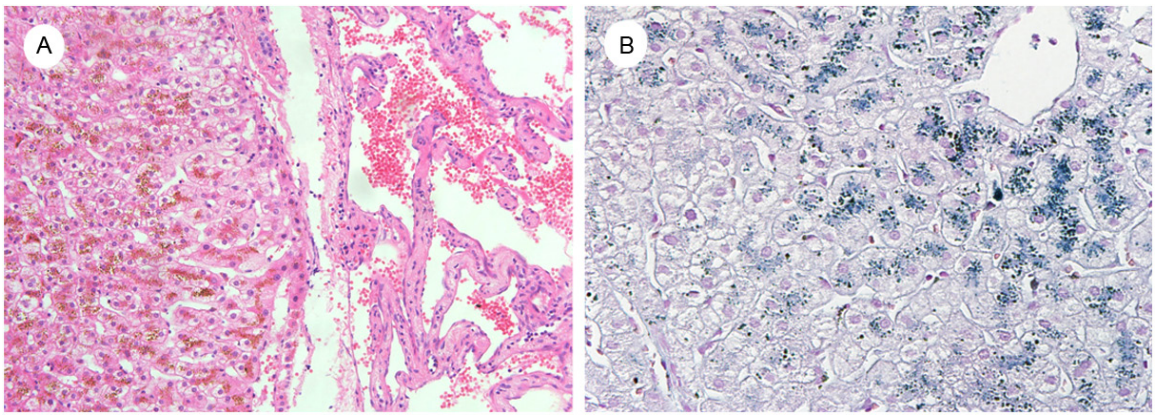

Figure 2. A. The tumor was composed of blood-filled vascular channels. The liver cells were laden with coarse brown granules with characteristic centrilobular distribution (HE ×100). B. The granules presented in the hepatocytes were stained blue-green with Schmorl staining for lipofuscin (×200).

sy in order to exclude the bile duct obstruction or other liver diseases, and the oral cholecystography also proved to be an effective way [5, 6].

DJS may also be associated with hepatobiliary disease or other autoimmune diseases, such as choledocholithiasis [7], viral hepatitis [8, 9], and systemic lupus erythematosus [10], but the present paper serves as the first report of DJS merging with liver cavernous hemangiomas. As the most frequent benign hepatic tumor, cavernous hemangioma is usually small, solitary or multiple, and asymptomatic but it can be large. In the majority of cases, these tumors are sporadic. Only a few studies in the literatures reported familial cavernous hepatic hemangioma charactered by the restriction to the female and autosomal dominant inheritance [11, 12]. We describe a more rare family in which two members from seven siblings presented cavernous hepatic hemangiomas and DJS simultaneously. The findings could support autosomal recessive inheritance as the mode of transmission of these tumors. But the true relationship between DJS and multiple liver cavernous hemangiomas in this case is unknown and needed for further study. Furthermore, three other cases of DJS with cavernous hemangiomas were diagnosed in our routine work for recent 2 years. However, for the limited clinical data, they were not helpful to identify the relationship induced by heredity or occasion.

As for the further therapy, no other particular treatment is necessary. Both of these two diseases have a relatively benign course, but establishing the diagnosis is important to spare patients from undergoing multiple unnecessary procedures and to exclude other more serious causes of hyperbilirubinemia. Symptoms would be precipitated or aggravated by surgical procedures, intercurrent disease and alcoholism.

Also this patient's sibling sister who shared same condition was reminded of the possible development of overt jaundice and icterus during her future pregnancy [13].

Conclusion

This is the first reported familial case of DJS with multiple liver cavernous hemangiomas. The relationship between DJS and hemangiomas remains unclear, and it might be contributed to some hereditary factors, or probably occurred simultaneously by chance. It was certified that the true reason for the long-term unclear jaundice was DJS, which was presumed clinically to be caused by bile excretion obstacles associated with the hemangiomas. Liver biopsy and histochemical stain may be helpful to identify the reason of jaundice and avoid misdiagnosis or an indefinite diagnosis.

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Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Disclosure of conflict of interest

None.

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