case report

Multiple hyperplastic nodular lesions of the liver in the Budd-Chari syndrome: a case report and review of published reports

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The Budd-Chari syndrome (BCS) is a group of disorders of hepatic vein outflow at various levels from the hepatic veins to inferior vena cave. We describe a 49-year-old man with multiple intrahepatic lesions who had been diagnosed with the BCS. The inferior vena cavography showed hepatic vein occlusion and long-range obstruction of inferior vena cava. The biopsy proved to be hyperplastic nodules, also called large regenerative nodules (LRNs). Both benign regenerative nodules and hepatocellular carcinoma (HCC) appear in patients with BCC; however, published reports about the diagnosis and differential diagnosis are limited. The incidence of HCC in patients with BCS varies greatly depending on geography. This case illustrates that benign nodules can arise in BCS patients. We reviewed published reports and speculated that medical procedures leading to portal perfusion decrease may be associated with the development of these hyperplastic nodules.

The Budd-Chari syndrome (BCS) is a group of disorders characterized by hepatic venous outflow obstruction at the level of the hepatic veins, the inferior vena cava.[1] Both benign and malignant hepatic nodules rise in a patient with BCS. However, there are limited published reports that describe in detail the differential diagnosis and management.[2-4] We experienced a 49-year-old man with multiple hyperplastic nodular hepatic lesions who had received meso-cavo-atrial shunt (MCASs) for the BCS. This patient was followed up for 1 year. This report discusses hepatic nodules in patients with the BCS after a review of published reports.

CASE

A 49-year-old man was admitted to our hospital for the evaluation of abdominal mass.

His past medical history was relevant for BCS. Eight years ago, the patient was referred to our department for varicose vein on the abdominal wall. The physical examination was significant for both lower extremities edema and abdominal distention. The diagnosis of BCS was suspected. The inferior vena cavography showed hepatic vein occlusion and long-range obstruction of inferior vena cava (**Figure 1**). Tests for deficiencies of protein C, protein S, antithrombin III, or factor V Leiden mutation were all negative. He was diagnosed with the combined BCS, and received the MCAS. The clinical symptoms relived after the surgery. The patient received the ultrasonography per 6 months.

On admission, the physical examination was significant for an enlarged liver palpable 10 cm below the costal margin and an enlarged spleen. The ultrasonography revealed the patent's artificial vessels and ascites. The contrast-enhanced computed tomography (CT) scan showed multiple, small, hypervascular lesions that had marked homogeneous enhancement during the arterial phase without washout in the portal phase and delayed phase (**Figures 2 and 3**). Hematologic investigations confirmed the decreased values of serum hemoglobin (99 g/L), platelets (71 000/mmc), and WBC (2400/mms). Alanine amino transferase and aspartate amino transferase were 14 and 26 IU/L; total bilirubin was 36.2 µmol/L. Serum total protein was 48.9 g/L (albumin 29.6 g/L), activa-

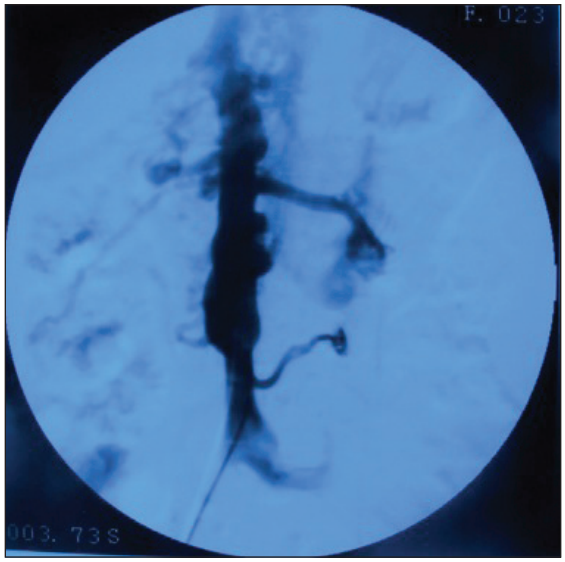

Figure 1. Inferior vena cavography showing hepatic vein occlusion and obstruction of inferior vena cava.

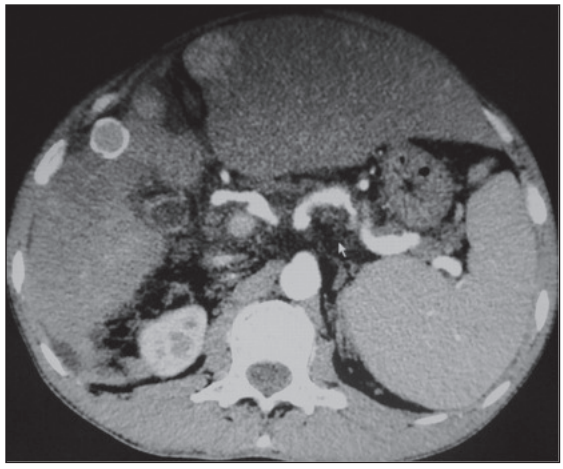

Figure 2. Contrast-enhanced computed tomography scan showing multiple, small, hypervascular lesions.

ted partial thromboplastin time was 48.4 seconds, and fibrinogen was 2.17 g/L. Hepatitis B and C were all negative. The α-fetoprotein (AFP) level was 2.2 ng/mL, which is considered normal. Indocyanine green retention at 15 minutes was 42.3%.

The patient had one of the largest lesions biopsied, which were histologically proven to be hyperplastic nodules (**Figure 4**). In this report we use the term "large regenerative nodules (LRNs)" to refer to these nodules.[5] During the follow-up period for 6 months, there was no notable change in size, and the patient stayed in good condition.

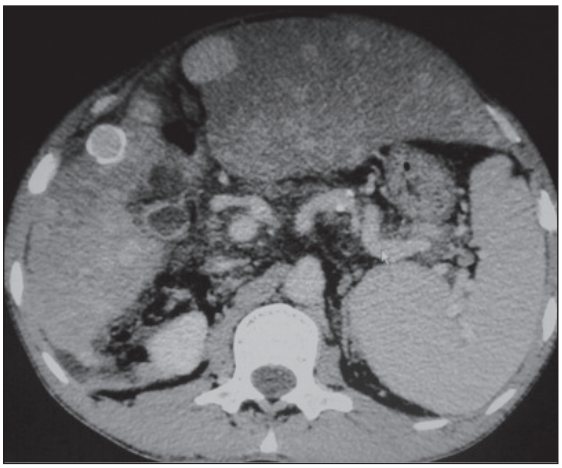

Figure 3. Contrast-enhanced computed tomography scan showing hypervascular lesions with marked homogeneous enhancement.

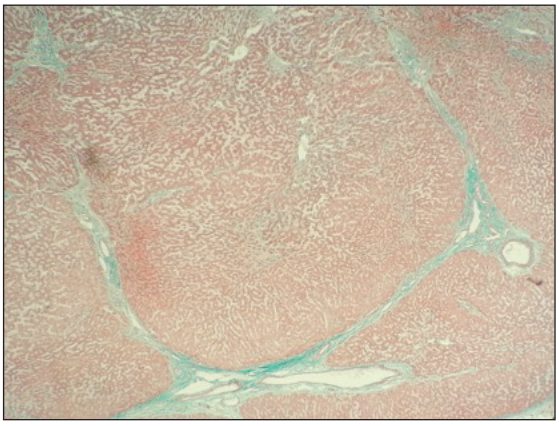

Figure 4. Histologic section showing hyperplastic nodules.

DISCUSSION

The BCS is a group of disorders of hepatic vein outflow at various levels from the hepatic veins to inferior vena cave (IVC).[1] The BCS can be hepatic vein obstruction, IVC obstruction, and combination of the two. The clinical presentation and prognosis differ depending on the type of the BCS.

The case is interesting for multiple hepatic nodules discussed only in a few published reports. Both benign regenerative nodules and hepatocellular carcinoma (HCC) appear in patients with BCS.[2,3,5-11] The differential diagnosis is difficult.

The pathogenesis and pathology of these benign nodules have not been well illustrated yet. Ibarrola et al. overserved 24 nodules in 4 explanted livers histologically, of which 11 were categorized as large regenerative

nodules, 7 as focal nodular hypoplasia–like nodules, and 6 as adenoma-like nodules.[8] Tanaka, M et al proposed to name these nodules as LRNs, and they gave a likely pathogenic explanation of a sequence: ischemia and hepatic insufficiency; elevation of hepatocellular growth factors; hepatocellular growth in regions of relatively good hepatic veins drainage; and new arterial growth.[5] This suggestion was supported by studies of Ibarrola et al. and Cazals-Hatem et al.[8,12] To our knowledge, there is no report about the malignant transformation of these benign nodules.

In this case, the patient received the MCASs resulting in a decrease of the portal perfusion. There are also reports of benign hepatic nodules in BCS patients who characterized as end-to-side portacaval shunting, transjugular intrahepatic portosystemic shunt,[13] and congenital absence of portal vein.[14] These patients shared a common character of lessening portal perfusion. Once the portal perfusion decreases, a compensatory dilation of artery occurs. The arterial hyperemia creates nodular reactive hepatocyte hyperplasia sequentially, which may evolve into regenerative nodules finally. The MCASs may act as a trigger factor

The incidence of HCC in patients with BCS varies greatly from 4.6% to 47.5% depending on geography. Several series have indicated that the membranous obstruction of IVC (MOVC) is frequently complicated by HCC.[2,9,18,19] The pathogenesis has not been well elucidated yet. Kage et al reported that cases of MOVC showed a congestive liver with extensive centrilobular necrosis, congestive liver fibrosis, or congestive liver cirrhosis on histologic examination, suggesting an increased regenerative activity.[15] Gwon et al suggested that chronic liver injuries and congestion might contribute to a fiberoptic process and the development of the nodular type of HCC.[16] It has been postulated that prolonged congestion due to MOVC causes hepatocellular necrosis and regeneration over many years, thereby rendering hepatocytes more susceptible to one or more environmental carcinogens such as hepatic virus infection and aflatoxin. It is interesting to note that HCC is rarely reported on patients with hepatic veins involved only. MOVC has a commonly chronic course, and a congestive liver state may lead to HCC. However, patients with hepatic veins involved only have commonly an acute or a subacute course. Matsui et al thought that the different course and period of the underlying disease result into different mobility of HCC.[18]

Sometimes, it is difficult to distinguish the LRNs and HCC because both of them are hypervascular lesions radiologically. However, the former tend to be multiple in number, relatively uniform in size (0.5-7 cm), homogeneous, and without washout in the portal phase.[3,4,17-19] On magnetic resonance imaging (MRI), the LRNs often reveal hyperintensity on T1-weighted images and hypointensity on T2-weighted images.[3,17] Vilgrain et al suggested that the hyperattenuation of nodules on unenhanced CT might be suggestive of benignity. However, this was not favored by Maetani's series. Peripheral rim and central scar in large nodules was also observed.[3,19] Maetani et al suggested that the central scar may be a distinctive symptom of benign nodule.[17]

Moucari et al[2] retrospectively reviewed 97 consecutive patients with BCS. Hepatic nodules were found in 43 patients, 11 of whom were diagnosed with HCC. Increased levels of serum AFP were accurate in distinguishing HCC from benign hepatic nodules for a cutoff level of 15 ng/mL. Therefore, serum AFP levels may be a useful screening tool for the surveillance of HCC.

In conclusion, the case illustrates that LRNs can arise in patients with BCS and HCC. The differential diagnosis from HCC is crucial but difficult. The former tends to be multiple in number, relatively uniform in size (0.5-7 cm), and homogeneous. The multi-phase contrast-enhanced CT, MRI, and AFP are all useful in distinguishing diagnose. Decrease of portal perfusion and increase of arterial supply may be a candidate mechanism of the LRNs. We speculate that medical procedures leading to portal perfusion decrease can act as a trigger factor in the development of the LRNs, so it is worth our attention.

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