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Liver cirrhosis caused by chronic Budd–Chiari syndrome

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Abstract

Chronic Budd–Chiari syndrome (BCS) is a rare cause of liver cirrhosis (LC) and tends to be misdiagnosed in clinical practice. In order to characterize LC caused by chronic BCS, we conducted this retrospective observational study. Medical records of all patients who were initially diagnosed as chronic BCS with LC when discharged from our department from January, 2011 to October, 2016 were reviewed. Cirrhotic patients with known causes and cases lacked key data were excluded. Data of remaining patients was collected and analyzed. A total of 15 cases were included in this study. Patients with LC caused by chronic BCS were characterized by preserved liver function and prominent portal hypertension (PH). Abdominal distention and edema of lower extremities were most common initial manifestations. Intra- or extrahepatic collaterals on imaging studies were of great importance for differential diagnosis. Most of these patients received interventional angioplasty followed by anticoagulation with warfarin and survived without obvious complications of PH. Chronic BCS was a rare but important cause of LC and should always be considered in patients with chronic liver disease and so-called cryptogenic LC. Early diagnosis and timely treatment may improve outcome. Correct interpretation of imaging examinations was fundamental to avoiding misdiagnosis.

Abbreviations: BCS = Budd–Chiari syndrome, CT = computed tomography, DUS = Doppler ultrasonography, EGV = esophagogastric varices, HBV = hepatitis B virus, HCV = hepatitis C virus, HV = hepatic vein, IVC = inferior vena cava, LC = liver cirrhosis, MELD = Model for End Stage Liver Disease, MRI = magnetic resonance imaging, PH = portal hypertension.

Keywords: Budd–Chiari syndrome, diagnosis, liver cirrhosis, portal hypertension

1. Introduction

Liver cirrhosis (LC) is the end stage of chronic liver disease and has caused lots of health loss.[1] It is the most common cause of portal hypertension (PH) in adults, whatever the underlying liver disease is. The etiology of LC differs geographically and remains poorly described, including hepatitis B virus (HBV) or hepatitis C virus infection, excessive alcohol intake, nonalcoholic fatty liver disease, and so on.[2–5] These aforementioned causes of LC are usually considered in clinical practice and can be easily confirmed or otherwise ruled out by careful history taking and thorough laboratory tests.

However, vascular disorders of the liver, for example, Budd–Chiari syndrome (BCS), are relatively rare and tend to be misdiagnosed. The incidence and prevalence of BCS in China with the top 5 high-prevalence areas are estimated as 0.88/million per year and 7.69/million, respectively.[6] LC caused by vascular disorders of the liver is estimated at 0.57% (46/8080) in Southern China and among them BCS accounts for 0.38% (31/8080).[3] According to an epidemiologic survey carried out in 1990, the prevalence of BCS in Japan is estimated to be 2.4/million with about 20 new cases occurring every year and most cases are diagnosed at the chronic stage.[7] The incidence rate is similar in Korea[8] and Sweden,[9] whereas the prevalence rate varies between countries. Thus, LC caused by chronic BCS is more than estimated because of delayed diagnosis and should be paid enough attention by clinicians.

The clinical manifestations of BCS vary, depending on the location, extent, and rapidity of obstruction and existence of collaterals. The course of the disease can be fulminant, acute, subacute, and chronic,[10] ranging from asymptomatic incidental finding to fatal hepatic failure. It is not difficult to make a diagnosis of BCS in typical patients. However, BCS can be totally asymptomatic or untypical for a long course and left untreated until progressing into LC and go a rapid downhill when PH finally develops. Sometimes, "cryptogenic liver cirrhosis" may be considered by inexperienced doctors. It is not rare to see patients receiving symptomatic treatment for PH and LC for several years while left BCS untreated. Significant morbidity and mortality can

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occur if without timely diagnosis and disease-specific management. Thus, we conducted this retrospective study to characterize LC caused by chronic BCS in order to avoid misdiagnosis and improve outcome.

2. Material and methods

2.1. Study population

The present was a retrospective observational study. Medical records of all patients who were diagnosed as chronic BCS as well as LC when discharged from our department between January, 2011 and October, 2016 were reviewed. Those diagnosed as LC caused by chronic BCS were included in this study. The exclusion criteria were as follows: missing of key data (esp. liver function and coagulative function), previously diagnosed as LC with known causes (e.g., HBV infection, excessive alcohol intake, etc), secondary BCS (e.g., with known hepatic malignancy). General information and clinical data were collected for further analysis. This study was approved by the Ethics Committee of Affiliated Drum Tower Hospital of Nanjing University Medical School.

2.2. Diagnosis of LC and BCS

According to the diagnostic criteria recommended by Suk et al, diagnosis of LC was based on history of chronic liver disease, typical physical findings, laboratory tests, cirrhotic changes on imaging studies (ultrasonography, computed tomography [CT], or magnetic resonance imaging [MRI]) and presence of PH (e.g., splenomegaly, ascites, and esophagogastric varices [EGV]). Liver biopsy was not always necessary while transjugular liver biopsy or percutaneous liver biopsy guided by ultrasonography would be considered if the diagnosis of LC was uncertain.[11,12] The severity of LC was assessed by Child–Pugh score and classification and Model for End Stage Liver Disease (MELD) score.

Diagnosis of BCS was based on the AASLD Practice Guidelines and EASL Clinical Practice Guidelines for vascular disease of the liver,[13,14] focusing on demonstrating obstruction of hepatic venous outflow tract by imaging examinations. Doppler ultrasonography (DUS) was the initial technique of choice because of its noninvasiveness and high sensitivity and specificity. Hepatic veins (HVs) and Inferior Vena Cava (IVC) devoid of flow signal and collateral circulation indicated BCS.[15] CT and MRI were auxiliary in demonstrating the general condition of abdomen, especially perfusion of hepatic parenchyma and collaterals. Important findings included heterogeneous patchy enhancement of the liver, nonvisualization of HVs, intra- and extrahepatic collaterals and obstruction of HVs/IVC. Classification of BCS depended on ultrasonography, CT/MRI, and venography of HVs/IVC. All patients were divided into 3 types: HVs, IVC, and HVs + IVC. Venography of HVs and/or IVC combined with venous pressure measurements was performed to confirm the diagnosis of BCS.

2.3. Treatment and outcome

Therapeutic modalities during hospitalization in our department were recorded. Subsequent treatment and outcome were followed by phone calls until October 31, 2016.

2.4. Data analysis

Continuous variables were expressed as median (range). Specific number and percentage were reported in tables.

3. Results

3.1. Patients and baseline features

During January, 2011 and October, 2016, a total of 2539 patients were diagnosed with LC and 23 of them were initially diagnosed as BCS in our department when discharged. Among them, 3 patients were ruled out for missing of key data, 5 patients for cirrhosis caused by HBV-infection or excessive alcohol intake. Data of the remaining 15 patients who were diagnosed as LC with unknown cause on admission but finally confirmed as chronic BCS were used for further analysis. General features and baseline laboratory results of the 15 patients were shown in Tables 1 and 2, respectively. Median follow-up time was 21.72 (1.58–59.04) months.

Most patients were male in their 50s, living within or near the Huanghuai Region. Median period from the likely onset to admission was more than half a year, with the longest as 20 years. Hypersplenism was common and more than half of these patients had pancytopenia or thrombocytopenia, while moderate anemia was only seen in patients with history of esophagogastric variceal bleeding. Elevation of bilirubin was not uncommon but seldom caused clinically significant jaundice. Liver function was generally preserved, indicated by Child–Pugh score and MELD Score. Tumor marker carbohydrate antigen 125 was elevated in most cases, which was mainly associated with ascites.

3.2. Clinical manifestations on admission

Initial symptoms of the 15 patients varied from asymptomatic incidental finding to life-threatening gastrointestinal bleeding (shown in Table 3). Most of them presented as abdominal distention (66.7%) and edema of lower extremities (60.0%). None of them reported abdominal pain and varices of lower extremities. Remarkable signs like pigmentation of lower extremities (26.7%) and varices of thoracic and abdominal wall (26.7%) could also be noted. Some patients had no specific symptoms on admission and were screened for LC because of incidental endoscopic finding of EGV, while for other some, hematemesis or melena was the initial symptom.

3.3. Evaluation of LC and PH

Abnormal shape and density of the liver were reported by image examinations in all cases (Table 4). Some of these patients

Table 1

General features of patients with cirrhosis caused by chronic Budd–Chiari syndrome.

	n	%
Age, y	52.5 ± 11.7 (36–73, median 53)	–
Gender (male:female)	11:4	73.3:26.7
Disease course	20 days–20 years	–
Smokers	3	20.0
Alcoholics	3	20.0
HBs-Ag	0	0
HBs-Ab	3	20.0
HBe-Ab	0	0
HBc-Ab	2	13.3
HCV-Ab	0	0
Diabetes mellitus	2	13.3
Hypertension	4	26.7

HCV = hepatitis C virus.

Table 2

Baseline laboratory results of patients with cirrhosis caused by chronic Budd–Chiari syndrome.

	Median (range)	Number of cases outside normal range n, %
White blood cell, $\times 10^9$/L	3.9 (2.1–7.7)	8 (53.3)
Hemoglobin, g/L	118 (71–152)	9 (60.0)
Platelet, $\times 10^9$/L	83 (38–186)	10 (66.7)
Alanine transaminase, U/L	21.8 (8.7–37.9)	0
Aspartate transaminase, U/L	28.9 (11.6–46.3)	3 (20.0)
Alkaline phosphotase, U/L	87.8 (50.2–145.8)	0
Gamma-glutamyl transpeptidase, U/L	84.2 (28.9–185.4)	11 (73.3)
Total bilirubin, μmol/L	21.8 (8.9–61.5)	10 (66.7)
Combined bilirubin, μmol/L	10.1 (3.5–41.6)	11 (73.3)
Albumin, g/L	36.8 (25.6–46)	3 (20.0)
Cholinesterase, kU/L	4.9 (1–8.8)	4 (26.7)
Blood urea nitrogen, mmol/L	5.1 (3.7–6.6)	0
Creatinine, μmol/L	57 (28–84)	1 (6.7)
Estimated glomerular filtration rate (n = 5)	121.9 (108.3–167.3)	0
Prothrobin time, s	13.8 (12.2–17.3)	2 (13.3)
Activated partial thromboplastin time, s	32.9 (30.3–55.4)	2 (13.3)
Fibrinogen, g/L	2.3 (1.5–2.8)	5 (33.3)
Alpha fetal protein, ng/mL	3.3 (0.7–7.6)	0
Carcinoembryonic antigen, ng/mL	1.08 (0.01–2.48)	0
Carbohydrate antigen 125, U/mL (n = 13)	60 (10.5–399.1)	9 (69.2)
Carbohydrate antigen 199, U/mL (n = 13)	11.8 (3.17–151.8)	1 (7.7)
Child–Pugh score	6 (5–13)	–
Child–Pugh class		
A	–	8 (53.3)
B	–	5 (33.3)
C	–	2 (13.3)
MELD score	10 (8–14)	–

MELD = Model for End Stage Liver Disease.

showed hepatomegaly rather than atrophy of the liver. Most of them had significant PH, with splenomegaly (13/15, 86.7%) and ascites (12/15, 80.0%) very common on DUS and CT/MRI. A total of 11 cases reported EGV on CT, and 4 of them were confirmed by endoscopy. Of all, 3 patients presented as variceal bleeding on admission and 2 of them had already received endoscopic therapy before admission. Intrahepatic or extrahepatic collaterals existed in almost all patients (14/15, 93.3%). Most of them were reported by other hospitals as chronic liver injury on ultrasonography and were more likely to be reported as LC on CT/MRI.

Table 3

Clinical manifestations on admission.

	n	%
Asymptomatic	2	13.3
Abdominal pain	0	0
Abdominal distension	10	66.7
Edema of lower extremities	9	60.0
Pigmentation of lower extremities	4	26.7
Varices of lower extremities	0	0
Jaundice	4	26.7
Hematemesis or melena	3	20.0
Varices of thoracic and abdominal wall	4	26.7

Table 4

Evaluation of liver cirrhosis and portal hypertension.

Imaging examination	n	%
Abnormal shape and density of the liver	15	100
Abnormal hepatic veins and/or inferior vena cava	15	100
Hepatomegaly	4	26.7
Splenomegaly	13	86.7
Ascites	12	80.0
Esophagogastric varices	11	73.3
Intrahepatic or extrahepatic collaterals	14	93.3
Chronic liver injury (reported)	4	26.7
Liver cirrhosis (reported)	14	93.3

3.4. Diagnosis of BCS

More than half of the 15 patients got the diagnosis of BCS at least half a year (20 days to more than 20 years) after initial presenting and did not receive timely etiologic treatment for BCS. Most of them were diagnosed as chronic liver disease or LC (93.3% in total) at local hospital and received symptomatic treatment for ascites, edema of legs, abnormal liver function, and so on. In 1 extreme case, BCS was not diagnosed until 20 years later. Usually, BCS was not suspected until abnormal IVC and/or HVs were finally noted on image examinations, though LC or chronic liver injury had already been treated long before. For these untypical BCS patients at the chronic stage, typical changes could be noted after reading the enhanced CT/MRI images carefully by experienced physicians, including heterogeneous enhancement of the liver parenchyma, obstruction of IVC and/or HVs, and intrahepatic or extrahepatic collaterals. To confirm the diagnosis of BCS, 13 of the 15 patients received IVC and/or HV venography. IVC type (6/15) was slightly more than HV type (5/15). Combination of IVC and HV obstruction (4/15) were also common. None of these patients received liver biopsy to confirm the diagnosis of BCS and LC. Besides, underlying cause of BCS (vascular abnormality or thrombosis) and possible risk factors of hypercoagulable state (such as protein C deficiency, myeloproliferative disease, anticardiolipin antibodies and so on.) were not clearly reported.

3.5. Treatment of BCS

Six patients received symptomatic treatment during hospitalization and the rest 9 received endovascular intervention. Percutaneous balloon plasty was performed in 9 patients to recanalize the obstructive IVC and/or HVs, 3 of them received combined endovascular stent placement. Pressure of IVC before and after percutaneous balloon plasty/endovascular stent placement was 25.67 and 19.33 cm H_2O, respectively. None of these patients received transjugular intrahepatic portosystemic shunt or liver transplantation up to their last follow-up. Endoscopic therapy for EGV was applied in 1 patient to prevent recurrent variceal bleeding (Table 5).

3.6. Follow-up and prognosis

All the 15 patients were contacted by phone calls, and 3 of them lost follow up. One patient with severe hypoalbuminemia and spontaneous bacterial peritonitis developed hepatic encephalopathy during hospitalization. He was finally transferred to another tertiary hospital after symptomatic treatment in our department and received embolectomy of IVC followed by endovascular

Table 5

Treatment of Budd–Chiari syndrome.

Symptomatic treatment	40% (6/15)
Inferior vena cava	0
Hepatic veins	4
Inferior vena cava + hepatic veins	2
Intervention	**60% (9/15)**
Percutaneous balloon plasty	6
Percutaneous balloon plasty + stent	2
Percutaneous balloon plasty + stent + endoscopic therapy	1

thrombolysis there but died 11 days later because of poor general condition. Another patient went to the same tertiary hospital and received endovascular balloon plasty followed by anticoagulation with warfarin. These 11 patients got symptoms relieved after treatment and survived with sound quality of life. Reobstruction was not clear because only a few of them had postprocedure review of the liver and IVC/HVs in the clinic. None of them reported development of hepatic carcinoma up to the last follow-up on October 31, 2016.

4. Discussion

As one of the vascular disorders of the liver, BCS is a heterogeneous group of clinical conditions presenting with hepatic venous outflow tract obstruction. Level of the obstruction can be located from the small HVs to the junction of IVC with the right atrium.[16] Cause of BCS is usually multifactorial, mainly including anatomical abnormalities and thrombosis. It can be divided into primary and secondary BCS, or be classified according to the location of obstruction: HVs, IVC, and combination of both. The prevalence and pathogenesis of primary BCS are quite different between Eastern and Western countries.[17] Generally, pure idiopathic membranous obstruction of IVC or combined IVC/HVs is predominant in Asia, while thrombosis of HVs is more common in West. For primary BCS, at least 1 underlying prothrombotic factor can be found in Western patients,[18,19] including congenital or acquired thrombophilia. However, those risk factors were rarely demonstrated in Chinese patients.[20] None of the patients in this study has fully screened for risk factors of hypercoagulable state such as protein C deficiency, myeloproliferative disease, anticardiolipin antibodies, and so on. More attention should be paid to underlying causes of BCS by clinicians and recommendations of well recognized guidelines should be followed to make a comprehensive diagnosis.

BCS is essentially a type of hepatopathy and can also develop into LC at advanced stage if left untreated. It is a rare cause of LC and tends to be ignored in clinical practice, especially by inexperienced doctors. As the pathogenesis of cirrhosis in BCS is quite different from cirrhosis caused by other etiologies, so do the principle and modalities of treatment. Therefore, early diagnosis is fundamental to timely treatment. It is worthwhile to characterize LC caused by chronic BCS in order to avoid misdiagnosis and improper treatment; thus, we conducted this retrospective study. Actually, it is not so difficult to identify BCS in patients with LC if following aspects could be considered carefully.

First of all, detailed history and physical examination of patients are always in the first place. BCS should always be considered if common causes of LC are ruled out. In contrast, known causes of LC (e.g., HBV infection or excessive consumption of alcohol) cannot exclude the possibility of BCS. PH in BCS is unspecific and occurs early, which seems to be inconsistent with liver function. Abdominal distention and ascites are common while gastrointestinal bleeding could be the only initial symptom in some cases. Varices of thoracic and abdominal walls, edema, varices, and pigmentation of lower limbs provide a clue and should not be overlooked. However, even if these signs are noted by doctors, BCS can still be misdiagnosed as dermatosis, purpura, vasculitis, or varicose vein of lower limbs before liver disease is considered. In this study, cirrhosis caused by chronic BCS manifests as generally preserved liver function. These patients are relatively young and most of them are generally in good condition. Liver function can be slightly abnormal and jaundice can be noted, but serum total bilirubin is no more than 4 mg/mL in this group of patients. Most patients have nearly normal coagulative function.

Next, imaging examination is of particular importance to the diagnosis of BCS, especially for patients with insidious symptoms because hypersplenism and liver dysfunction in BCS are unspecific. Ultrasonography of the liver and the spleen is essential, especially in patients with abnormal liver function and thrombothytopenia. BCS is relatively easy to be ruled out by DUS while CT/MRI could help to make a diagnosis when uneven density and abnormal vessel changes of the liver are noted. In fact, most misdiagnosed BCS cases could have been avoided if physicians and radiologist did not turn a blind eye to typical image features of BCS itself. Actually, the diagnosis could be delayed for as long as several years even if chronic liver disease or LC has already been confirmed and treated. The diagnosis of cryptogenic LC should be made cautiously and special attention should be paid to vessel changes and enhancement features of the liver on CT and MRI. Patency of HVs and IVC on imaging examinations is sufficient to rule out BCS. DUS combined with CT/MRI is enough to diagnosis BCS in most cases. Indeed, LC caused by BCS is somewhat difficult to be differentiated from cirrhosis caused by other etiologies. Morphological changes of the caudate lobe and the enhancement pattern of liver parenchyma are significantly different between LC caused by HBV infection and BCS. Peng et al have investigated the imaging features of collateral circulation in BCS and Hepatitis B related LC on CT and demonstrated that caudate lobe enlargement is more common in LC cause by BCS than in LC caused by HBV infection (11/15 vs 5/60, 73% vs 8%). Intra- and extrahepatic venous collaterals are common in BCS and are not detected in patients of LC caused by HBV infection,[21] which is in accordance with our findings. Jeng et al[22] recommend maximum-intensity projection and minimum-intensity projection of CT images as simple and effective techniques to establish the diagnosis of BCS, especially in complicated cirrhotic patients, thereby avoiding invasive interventional procedures. Liver biopsy is not routinely operated but should be considered in complicated cases if imaging has failed to demonstrate obstruction of large veins.[14]

Last but not least, BCS should be differentiated from hepatic veno-occlusive disease and hepatic outflow obstruction secondary to cardiac and pericardial diseases which will also cause chronic congestive liver injury. Careful history taking is crucial to identifying heart disease or history of herbal ingestion. Physical examination is also necessary to find edema and/or pigmentation of lower extremities, varices of thoracic and abdominal walls, jaundice, hepatomegaly, and so on. However, sometimes congestive enlargement of the liver (esp. the caudate lobe) makes the IVC seems to be obstructed, thus making it hard to differentiate from hepatic veno-occlusive diseases. Map-like

enhancement of hepatic parenchyma is typical of hepatic veno-occlusive diseases, while obstructive signs of HVs/IVC on CT/MRI are helpful to diagnose BCS, including expansion of distal vessels and intrahepatic or extrahepatic collaterals.[23] Pigmentation of lower extremities and varices of thoracic and abdominal walls also indicate BCS and echocardiography helps to rule out cardiac and pericardial diseases.

In short, correct diagnosis is the premise for proper treatment. It is important for clinicians to realize the possibility of LC caused by vascular disease of the liver and provide timely etiologic treatment. According to our study, most of these patients have received merely symptomatic treatment and BCS is left untreated. It is not uncommon to see patients suffering from recurrent ascites and gastrointestinal bleeding before finally diagnosed as BCS. In extreme cases, it can be life-threatening, especially when complications of advanced LC emerge.[24] Therapeutic strategies of LC caused by BCS are not the same as that caused by other common etiologies. A stepwise treatment has been recommended currently, from anticoagulation, thrombolysis to endovascular intervention, portosystemic shunt, and even liver transplantation. In our study, most patients improved after endovascular intervention followed by anticoagulation and no patients received transjugular intrahepatic portosystemic shunt or liver transplantation until last follow-up. Most of the patients of BCS in China have obstructed IVC with or without involving HVs and are usually diagnosed at the chronic stage. Collateral circulations have already developed and most of them are hemodynamically compensated. Recanalization of IVC by percutaneous angioplasty with balloon and stent as first-step treatment could achieve satisfied outcome in most cases, so that more advanced modalities such as transjugular intrahepatic portosystemic shunt are rarely applied. Nevertheless, complications of PH should be treated according to well recognized guidelines. PH and liver function can be improved after early and effective treatment and long-term outcome of BCS is generally satisfied.[18,25–30] After interventional treatment for BCS, most of our patients have survived without notable symptoms of PH. Long-term survival of these patients is not clear because short follow-up duration, and it is also rarely reported elsewhere. According the systemic review conducted by Qi et al[31], the median 1-, 5-, and 10-year survival rate of BCS in the last decade are 90%, 82.5%, and 72%, respectively. Besides, none of these patients have developed hepatic carcinoma during follow-up, which may be partly due to short follow-up time period and small sample size. In fact, incidence of hepatic carcinoma in patients with BCS is not uncommon in China and should be screened regularly during follow-up.[32–34]

Due to limited cases of our study, the results reported here may not be extrapolated but could still remind clinicians not to misdiagnosis BCS in LC. In conclusion, for cirrhotic patients with unknown cause, especially those with prominent PH but preserved liver function, chronic BCS should always be considered. Early diagnosis and timely treatment may improve outcome. Correct interpretation of imaging examinations is vital to avoid misdiagnosis.

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