Clinical and Histological Features of Different Types of Budd-Chiari Syndrome: A Comparison of 4 Cases

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Key Words
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Abstract
Budd-Chiari syndrome (BCS) is a rare condition characterized by hepatic venous outflow obstruction. In this report, we present 4 cases of BCS with complete and incomplete obstruction of the inferior vena cava (IVC) and hepatic vein (HV). Each case showed different and unique features of liver damage, which were attributed to the site and degree of obstruction. Interestingly, improved liver functions such as increased serum albumin levels, decreased hyaluronic acid levels and a normal indocyanine green clearance test were evident within 1 month of the balloon angioplasty. Pericellular fibrosis and hypervascular regenerative nodules were also reversible after obstruction removal. Therefore, it is very important to manage this rare disease before it progresses to liver cirrhosis.

Introduction
Budd-Chiari syndrome (BCS) is characterized by the incomplete or complete obstruction of hepatic venous outflow, leading to liver damage caused by congestion and portal hypertension [1, 2]. BCS includes several conditions that lead to hepatic outflow obstruction from a hepatic vein (HV) branch to the junction of the inferior vena cava (IVC) and right atrium [3]. Thus far, several reports have described the clinical cause, imaging and pathological findings of BCS [4]. IVC obstruction with or without HV involvement is predominant in Asia; on the contrary, pure HV obstruction is reported more often in Western countries [1]. It is possible that the clinical manifestation differs between patients with HV branch obstruction and those with IVC obstruction. The degree of obstruction, such as a complete or partial obstruction of the HV outflow tract, may also affect the symptoms and clinical course of BCS [5]. We encountered 4 cases of BCS: 2 patients had HV obstruction and 2 patients had...
IVC obstruction. Interestingly, their clinical presentations varied from an asymptomatic condition to acute liver failure. In this report, we summarize the clinical courses and manifestations of these 4 cases of BCS and compare the unique radiological and histological findings, which were attributed to the degree and site of obstruction.

Our institution did not require institution approval or informed consent for review of patient records and images in the case report. We explained the research content and gave patients the right to refuse inclusion in our study.

**Case 1: Partial IVC Obstruction**

A 53-year-old woman had a 1-year history of leg edema, body weight gain and dyspnea. She was diagnosed with liver cirrhosis by liver biopsy at the first hospital she visited, and was prescribed diuretics after she gained 4 kg of body weight. The initial laboratory findings at our hospital were as follows: white blood cell count (WBC) 5,400/μl (3,500–9,800/μl); hemoglobin (Hb) 16.1 g/dl (11.3–15.5 g/dl for women); platelet count (PLT) 146,000/μl (155,000–365,000/μl); albumin 3.3 g/dl (3.9–4.9 g/dl); total bilirubin 0.8 mg/dl (0.3–1.3 mg/dl); alkaline phosphatase (ALP) 182 IU/l (115–359 IU/l); aspartate aminotransferase (AST) 30 IU/l (10–40 IU/l); alanine aminotransferase (ALT) 25 IU/l (≤35 IU/l); prothrombin time (PT; activity percentage) 80% (≥82%); activated partial thromboplastin time (aPTT) 30.8 s (25.5–36.1 s); hepatitis B surface antigen (HBsAg) negative; hepatitis C antibody (HCVAb) negative; antinuclear antibody (ANA) negative; antimitochondrial antibody (AMA) negative; anti-liver kidney microsomal antibodies negative; hyaluronic acid 69 ng/ml (≤50.0 ng/ml); type III procollagen-N-peptide 0.7 U/ml (≤1.0 U/ml); type IV collagen 7S domain 7.7 ng/ml (≤5.0 ng/ml); indocyanine green clearance test (retention at 15 min; ICG R15) 13.9% (≤10%). Serum protein C and protein S levels were normal, and lupus anticoagulant and anticardiolipin antibodies (ACA) were negative. Contrast-enhanced computed tomography (CE-CT) performed at our hospital revealed atrophy of the right lobe of the liver with enlargement of the caudate lobe (fig. 1a). Collaterals and dilation of the vertebral venous plexus and azygos vein were observed (fig. 1b). Catheter venography revealed incomplete IVC obstruction at the diaphragm level (fig. 1c). Needle liver biopsy showed stasis of the hepatic sinusoid surrounding the central vein and bridging fibrosis were observed. Pathological examination revealed incomplete membranous obstruction of the IVC at the diaphragm level (white arrow).
biopsy was performed and histology showed dilation and stasis of the hepatic sinusoid with bridging fibrosis (fig. 1d). Four months after occlusion removal by balloon angioplasty the liver function test was improved with improvement of the patchy enhancement of the liver parenchyma (fig. 1e) and regression of collaterals (fig. 1f). Serum hyaluronic acid levels had dropped to 27 ng/ml 1 month after the balloon angioplasty. However, liver atrophy was still observed (fig. 1e) and ICG R15 was still increased (20%).

**Case 2: Complete IVC Obstruction**

A 48-year-old woman visited a private clinic because of lower leg myalgia. She had a 3-year history of leg edema and abdominal fullness. When she visited the hospital, liver damage was confirmed with biochemical blood examination. Ascites and esophageal varices were also detected and diuretics were prescribed. Leg edema and ascites improved after the administration of diuretics. Laboratory findings were as follows: WBC 5,600/μl; Hb 14.2 g/dl; PLT 169,000/μl; albumin 3.6 g/dl; total bilirubin 2.9 mg/dl; ALP 698 IU/l; AST 40 IU/l; ALT 41 IU/l; PT activity percentage 77%; aPTT 32.6 s; HBsAg negative; HCVAb negative; ANA negative; AMA negative; hyaluronic acid 37 ng/ml; type IV collagen 7S domain 11.4 ng/ml; ICG R15 25.0%. Protein C and protein S levels were normal. Lupus anticoagulant and ACA were negative. The initial CE-CT revealed patchy enhancement of the liver (fig. 2a). However, the liver surface was smooth compared to that of case 1, suggesting that the morphological change caused by liver fibrosis was not severe (fig. 2a). Catheter venography showed complete IVC obstruction caused by a membranous web at the diaphragm level accompanied by collateral vessels such as dilated azygos and hemiazygos veins and vertebral venous plexus (fig. 2b). Liver biopsy revealed dilation and congestion of the sinusoid around the central vein (fig. 2c). Extravasation of red blood cells into the liver cell plate and necrosis with congestion of the liver parenchyma were observed (fig. 2d). On the other hand, hepatic fibrosis was mild without badging fibrosis (fig. 2e). One month after balloon angioplasty, the patchy enhancement of the liver was improved (fig. 2f). Hyaluronic acid and ICG R15 serum concentrations were improved 1 month after the angioplasty (16 ng/ml and 14%, respectively).

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**Fig. 2.** Radiological and histological findings of BCS with complete IVC obstruction (case 2). a CE-CT (delayed phase) before the balloon angioplasty. b The catheter venography of the IVC showed complete membranous obstruction of the IVC (white arrow) with dilation of collateral vessels. c HE staining of the liver needle biopsy; dilation of the sinusoid and congestion around the central vein were detected. d Extravasation of red blood cells and necrosis. e Azan staining of the liver biopsy sample; fibrosis of the liver was mild. f CE-CT (delayed phase) 1 month after the balloon angioplasty.
Case 3: Complete IVC and HV Obstruction

A 22-year-old man presented to the hospital with a 2-week history of fever and dry cough. No abnormal finding was detected on chest radiographs and he was prescribed an antipyretic. The cough worsened and he also experienced nausea and abdominal discomfort. Mild proteinuria was detected by urine tests. Blood chemical tests at the time of admission showed liver damage as follows: WBC 5,300/μl; Hb 13.0 g/dl; PLT 163,000/μl; albumin 2.7 g/dl; total bilirubin 3.5 mg/dl; ALP 578 IU/l; AST 58 IU/l; ALT 83 IU/l; PT activity percentage 40.6%; hepaplastin test 41.1%; HBsAg negative; HCVAb negative; ANA negative; AMA negative; ICG R15 95.0%. IgM antibody against mycoplasma was positive. Protein C and protein S levels did not decrease. Lupus anticoagulant, ACA and anti-neutrophil cytoplasmic antibodies were negative. The patient’s fever improved after hospital admission. However, abdominal discomfort, pain and fullness worsened with persistent nausea. CE-CT revealed ascites and dilation of the azygos and hemiazygos veins (fig. 3a). A massive thrombus was present in the IVC extending from the level of the diaphragm to above the right renal vein, and involved the HV branches (fig. 3b), which reached the second lumbar level (fig. 3c, d). The IVC was completely occluded without any HV enhancement, suggesting the complete obstruction of all HV branches (fig. 3b–d). There was no radiological evidence of mass lesions or thromboemboli in the chest, abdomen or pelvis. Gastroduodenal endoscopy showed formation of esophageal varices, suggesting that partial obstruction of the IVC might be present before the onset of the symptom. During the clinical course, ascites and pleural effusion increased and liver function deteriorated. The patient was diagnosed with subacute BCS caused by thrombus. He was transferred to the specialized institution for liver transplantation.

Case 4: Partial HV Obstruction

A 53-year-old man presented to the hospital with a 3-year history of persistent leg edema and abdominal fullness with thrombocytopenia and hemorrhoids. Ascites...
was detected and diuretics were prescribed. He was referred to our hospital. Laboratory findings were as follows: WBC 6,600/μl; Hb 16.2 g/dl; PLT 149,000/μl; albumin 3.1 g/dl; total bilirubin 1.1 mg/dl; ALP 436 IUL; AST 44 IU/l; ALT 15 IU/l; PT activity percentage 116%; aPTT 27.8 s; HBsAg negative; HCVAb negative; ANA was positive at 1:80 dilution; AMA negative; hyaluronic acid 127 ng/ml; type IV collagen 7S domain 6.3 ng/ml; ICG R15 38.0%. Protein C and protein S levels were normal, and lupus anticoagulant and ACA were negative. CE-CT findings indicated heterogeneous enhancement of the liver parenchyma with intrahepatic venovenous collaterals from the middle to right HV (fig. 4a). CT angiography also revealed heterogeneous enhancement (fig. 4b), indicating the presence of reversed portal venous blood flow that should result from the increased postsinusoidal pressure produced by HV obstruction. Color Doppler sonography revealed complete obstruction of the left and middle HV. Incomplete obstruction of the right HV caused by a web was also detected by the sonography, portography and right hepatic venography (fig. 4c). The liver biopsy showed sinusoid dilation and marked pericellular fibrosis around the central vein (fig. 4d). After the balloon angioplasty and stent placement in the right HV, heterogeneous enhancement with the hypoattenuating portion of the liver parenchyma improved to homogeneous enhancement (fig. 4e). Histological findings of sinusoid dilation and pericellular fibrosis were also markedly improved (fig. 4f). The size and enhancement of the hypervascular regenerative nodule detected in the posterior segment by the initial CT gradually decreased during the 30 months after the angioplasty (fig. 4g). The detailed findings of this hyper-

**Fig. 4.** Radiological findings of BCS with incomplete HV obstruction (case 4). a CE-CT (portal phase) before the balloon angioplasty; the arrow indicates intrahepatic venovenous collaterals from the middle to right HV. b CT angiography showed heterogeneous enhancement of the liver. c The composition of the right hepatic venography and the catheter venography of IVC; the white arrow shows the membranous web of the right HV. d Masson’s trichrome staining of the liver biopsy sample before the angioplasty; sinusoid dilation and marked pericellular fibrosis were observed around the central vein. e CE-CT (delayed phase) 1 month after the balloon angioplasty; liver enhancement was homogeneous compared to the CT findings before the angioplasty (a). f Azan staining of the liver biopsy 1 month after the angioplasty; sinusoid dilation and pericellular fibrosis were markedly improved. g Decreased enhancement of the hypervascular regenerative nodule was shown 4, 17 and 30 months after the angioplasty.
vascular nodule before treatment were previously reported [6]. Hyaluronic acid and ICG R15 serum concentrations were markedly improved 1 month after the angioplasty (36 ng/ml and 22.0%, respectively) with increased serum albumin concentration (3.9 g/dl).

### Discussion

The clinical symptoms and radiological and histological findings of the 4 cases are summarized in Table 1. Case 1 represented an IVC obstruction. Venography showed incomplete obstruction along with azygos vein dilation. Therefore, it is possible that gradual but mild progression of liver congestion caused a chronic type of BCS, which led to altered morphology with liver cirrhosis [3]. In this case, liver cirrhosis did not improve after obstruction removal by balloon angioplasty, although the extrahepatic collateral vessel showed regression. On the other hand, the patient in case 2 showed complete IVC obstruction by web formation and elevated bilirubin concentration. The histology of case 2 showed milder fibrosis but more severe sinusoid stasis and necrosis with hemorrhage in the liver parenchyma. Therefore, complete IVC obstruction induced an earlier onset of symptomatic BCS without the finding of liver cirrhosis compared to case 1. The CE-CT finding of liver congestion disappeared and hyaluronic acid and ICG R15 serum concentrations improved after the angioplasty. Case 3 was regarded as an acute to subacute type of BCS because of the wide range of thrombosis in the IVC and HV [7]. Although progression of collateral veins such as dilated azygos and hemiazygos veins and the subcutaneous vein of the abdominal wall was observed, the large thrombus in the IVC and HV should have led to rapid progression of clinical symptoms with liver failure, which was a characteristic feature of this case, although we could not perform liver biopsy because of the deteriorated liver function. The patient in case 4 showed HV branch obstruction. Unique findings of CE-CT in this case were an intrahepatic venovenous shunt.

### Table 1. Comparisons of the clinical features of the 4 cases

<table>
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<td>IVC and HV complete</td>
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<td>Dilation of the vertebral venous plexus, azygos and hemiazygos veins</td>
<td>Dilation of the azygos and hemiazygos veins</td>
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</tr>
<tr>
<td>Histological findings</td>
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<td>Congestion of the sinusoid and necrosis with extravasation of red blood cells, mild fibrosis</td>
<td>N/A</td>
<td>Congestion and dilation of the sinusoid, pericellular fibrosis in the central portion</td>
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<td>N/A</td>
<td>Improvement of congestion and pericellular fibrosis, regression of the hypervascular nodule</td>
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N/A = Not available.
through the collaterals, which bypassed the obstructed branch, and characteristic patchy enhancement of the liver parenchyma in the obstructed segment [4]. However, progression of extrahepatic collaterals was minimal compared to that in the IVC obstruction type. Interestingly, pericellular fibrosis in the central lesion of the lobules (zone 3) could be reversed accompanied by improved hyaluronic acid and ICG R15 serum concentrations at 1 month after obstruction removal. As hyaluronic acid degradation mainly takes place in the sinusoidal endothelial cells [8], it could be reasonable to speculate that the rapid decrease in serum hyaluronic acid levels reflected the functional recovery of the endothelial cells that were damaged by liver congestion.

We presented 4 cases of BCS in this report, each of which showed a unique clinical course with unique radiological and histological findings. Although incomplete and partial obstruction of the IVC and HV branch might be asymptomatic and easily overlooked [2], obstruction removal before the establishment of liver cirrhosis is important to reverse liver function and liver fibrosis progression [9].

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Disclosure Statement

The authors have no conflicts of interest to declare.

References