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CASE REPORT

Severe acute cholestatic hepatitis of unknown etiology successfully treated with the Chinese herbal medicine Inchinko-to (TJ-135)

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Abstract

Severe acute hepatitis of unknown etiology is difficult to treat and often progresses to subacute fulminant hepatitis or late-onset hepatic failure. A 45-year-old well-nourished, healthy man had progressive fatigue and his liver function tests showed severe liver dysfunction. The etiology of sever acute cholestatic hepatitis was unknown. The liver function tests normalized gradually, which excluded high persistent total bilirubin after starting on predonine. A liver biopsy showed chronic active hepatitis with mild fibrosis (A2, F1). Oral Inchinko-to, a Chinese herbal medicine, at 7.5 g daily was prescribed. The treatment was effective with no adverse effects. We present a successfully treated case and discuss hepatoprotective and choleretic effects of Inchinko-to.

Key words: Acute cholestatic hepatitis; Etiology; Inchinko-to; Herbal medicine

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INTRODUCTION

Treatment of severe acute hepatitis of unknown etiology is difficult, and the disease often progresses to subacute fulminant hepatitis or late-onset hepatic failure[1]. Several studies have reported on the effectiveness of Inchinko-to, a Chinese herbal medicine used to treat liver disorders and jaundice in Japan[2-5]. Successful treatment of acute hepatic failure of unknown etiology with Inchinko-to has been reported[6].

We treated a patient who suffered from severe acute cholestatic hepatitis of unknown etiology with Inchinko-to. The treatment was effective with no adverse effects. We report and discuss the case.

CASE REPORT

The patient was a 45-year-old man, who had fatigue, vomiting, slight fever, and noticed that his urine had been darker than usual for 1 mo before visiting the clinic. He began to suffer from severe fatigue and loss of appetite, and thus visited the clinic. On physical examination, his skin was dark yellow, without a palpable liver. Liver function tests revealed severe liver dysfunction (Table 1). He was a well-nourished, healthy man with a history of duodenal ulcer. He did not drink alcohol and had no history of blood or blood products transfusion or the use of any drugs, including herbal medicine. He was exposed to no known environmental hazards. His older brother had non-alcoholic steatohepatitis and underwent surgery for rectal carcinoma. Abdominal ultrasonography showed a severely swollen gallbladder and normal intra- and extrahepatic bile ducts; the liver shape and architecture were normal. Upper endoscopy showed an edematous narrowing at the post-bulbar portion of the duodenum and a duodenal ulcer scar in the duodenal bulb.

He was admitted to the hospital. Ursodeoxycholic acid (UDCA) was started at 600 mg daily. Tests for hepatitis A, B, C, and E viruses, Epstein-Barr virus and cytomegalovirus were all negative. Autoantibodies were negative, including anti-mitochondrial, smooth muscle, antinuclear, and perinuclear anti-neutrophil cytoplasmic antibody. Gamma globulin was within the normal limits. The hemolytic complement activity (CH50) was elevated slightly. Abdominal computed tomography showed a severely swollen gallbladder, normal intra- and extrahepatic bile ducts, and normal liver shape and architecture (Figure 1, top). Magnetic resonance imaging showed an edematous,

Table 1 Laboratory data on admission

White blood cells (/μL)	4600	Alfa1 globulin (%)	4.2
Red blood cells (/μL)	493	Alfa2 globulin (%)	7.2
Hemoglobin (g/dL)	15.1	Beta globulin (%)	11.2
Hematocrit (%)	46	Gamma globulin (%)	15.3
Platelets (/μL)	16.7×10^4	CH50 (OU/mL)	52.4
Total protein (g/dL)	5.8	Anti-nuclear antibody	-
Albumin (g/dL)	3.5		
Total bilirubin (mg/dL)	6	P-ANCA	-
Direct bilirubin (mg/dL)	4.9	Anti-mitochondrial	-
AST (IU/L)	810	antibody	
ALT (IU/L)	1239	HA-IgM	-
LDH (IU/L)	418	HBs Ag	-
Alkaline phosphatase	687	HBs Ab	-
(IU/L)		HBe Ag	-
rGTP (IU/L)	305	HCV Ab	-
Prothrombin time (%)	92.9	HEV-IgM	-
Activated partial	29.2	HEV-IgG	-
thromboplastin time (s)		EBV-VCM	-
C-reactive protein (mg/dL)	1	CMV-IgM	-
NH_3 (mcg/dL)	70		

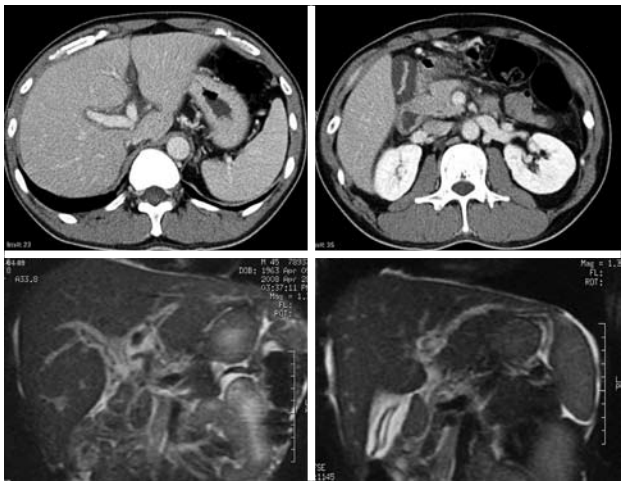

Figure 1 Abdominal CTs and MRIs on admission. Abdominal CTs showing normal liver shape and architecture, normal intra-and extrahepatic bile ducts, and a severely swollen gallbladder (top); MRIs showing a normal liver, bile duct, an edematous, thickened gallbladder wall, and periportal edema (bottom).

thickened gallbladder wall, periportal edema, slight ascites, and a normal liver, bile duct, and pancreatic duct (Figure 1, bottom). Based on these findings, the patient was diagnosed with severe acute cholestatic hepatitis of unknown etiology. The total bilirubin level continued to rise, and so the patient was started on predonine 20 mg daily on 7 May 2008. The serum aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels normalized gradually, while the total bilirubin remained high. Oral Inchinko-to at 7.5 g daily was prescribed on 17 May 2008. He was weaned from predonine. Subsequently, the total bilirubin level began to decrease (Figure 2). A liver biopsy showed chronic active hepatitis with mild fibrosis (A2, F1).

The patient was discharged. He is currently well at 12 mo after UDCA and Inchinko-to treatment.

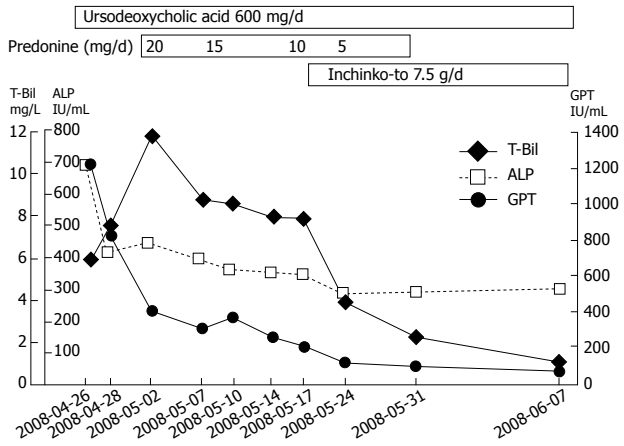

Figure 2 Clinical course of the patient.

DISCUSSION

Without evidence of a virus infection, autoimmune disease, alcohol or drug use, blood or blood products administration, and environmental hazards, the patient was considered to have severe acute cholestatic hepatitis of unknown etiology. Initially, predonine was prescribed for suspected autoimmune hepatitis with a high total bilirubin level[7]. The increasing total bilirubin was thought to suggest progression to subacute fulminant hepatitis[1]. Inchinko-to, a Chinese herbal medicine, has been used clinically for various liver diseases in Japan and China[2-5].

Recent experimental studies have clarified the molecular mechanism of hepatoprotective and choleretic effects of Inchinko-to and its ingredients, and have provided a good rationale for its clinical application to a wide variety of liver diseases, although there is no sound evidence with prospective randomized clinical studies[8-13]. The ingredients of Inchinko-to are genipin, 6,7-dimethylesculetin, capillin, capillene, and capillarisin[2,14,15]. Therefore, we decided to give Inchinko-to to our patient who suffered from severe acute cholestatic hepatitis of unknown etiology. The treatment was effective with no adverse effects.

The death of liver cells in hepatitis is thought to involve apoptosis[16]. Fas/FasL-mediated cytotoxicity is critical to hepatic injury, particularly fulminant hepatitis[17]. Genipin markedly suppressed liver apoptosis/injury in a lethal fulminant hepatitis model[9] and improved acute liver dysfunction by the suppression of tumor necrosis factor-α production[10]. In addition, capillin and capillene inhibit liver cell apoptosis induced by transforming growth factor[8].

Cholestasis results in hepatic and systemic accumulation of potentially toxic bile acids, resulting in liver damage and jaundice[18]. The altered expression of specific hepatocellular transport systems and profound changes in the cytoskeleton of the hepatocytes are associated with cholestatic liver disease[18]. In particular, the impairment of canalicular transport systems has a major role in the pathogenesis of acquired forms of intrahepatic cholestasis[18]. Inchinko-to exerts potent choleretic effects *via* a bile-acid-independent mechanism of multidrug-resistance-associated protein 2 mediation and glutathione content modulation[11-13] by genipin, and of constitutive

androstane receptor activation by 6,7-dimethylesculetin[12]. The marked reduction in bilirubin level after Inchinko-to administration in our case suggested that Inchinko-to and its ingredients stimulated and restored the impaired canalicular transport systems.

UDCA was also used in this case and it has been reported to be effective in cases of chronic liver disease[19] and prolonged cholestasis of acute hepatitis[20]. The therapeutic benefit of UDCA in the treatment of cholestasis may result from a combination of cytoprotective, antiapoptotic, immunomodulatory, and choleretic effects[21]. The choleretic effects of UDCA are medicated by up-regulation of canalicular transporter protein levels[22], and inhibit apoptosis by modulating mitochondrial function[23]. No apparent effect was observed on liver function tests in our case soon after the administration of UDCA. Therefore, the combination of Inchinko-to and UDCA possibly worked synergistically in improving the acute cholestatic hepatitis in this case.

Finally, our success in treating a patient with acute cholestatic hepatitis of unknown etiology supports a previous study[6], and suggests its efficacy in treating such liver disease. Our findings warrant a further clinical trial.

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