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# A Case of Autoimmune Hepatitis Associated with Veno-occlusive Disease and Primary Sclerosing Cholangitis

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A 53-year-old woman was admitted to our hospital because of liver dysfunction. Laboratory data and liver biopsy revealed autoimmune hepatitis (AIH) and veno-occulusive disease (VOD). Endoscopic retrograde cholangiopancreatography demonstrated bile duct changes consistent with primary sclerosing cholangitis (PSC). The clinical features and liver profile tests improved with predonisolone and ursodeoxycluic acid. This patient is a rare case initially presenting features of 3 different hepatic diseases; AIH, VOD and PSC. During her long clinical course, predonisolone was effective. This case may provide an insight in understanding autoimmune hepatic diseases.

**Key words**: veno-occlusive disease, autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, pericholangitis

## Introduction

Hepatic veno-occlusive disease (VOD) is a progressive form of portal hypertension, characterised histologically by hepatic central vein dilatation and fibrosis, which is a potentially fatal cause of ascites and hepatic failure. The cause of VOD has been reported to be exposure to plants (Jamaican *Crotalaria fular*) that contain hepatotoxic pyrrolozidine alkaloids[1)~6)]. Recently, many cases caused by radiation injury, bone marrow transplantation and high-dose chemotherapy have been reported[7)~11)].

We describe a patient with complicated autoimmune hepatic diseases including VOD who had a habit of drinking teas imported from China. To our knowledge, such a case has not been previously reported.

## Case

A 53-year-old woman was admitted to our hospital in a coma in July 1997. She had history of liver dysfunction since 1986. However, she had not taken any medication until August 1994 when she was admitted to our clinic because of arthralgia, liver dysfunction, thrombocytepenia and neutropenia. The patient did not drink alcohol regularly, and had a habit of drinking teas such as *Farfarae flos* (*bakkenlide*), *cordyceps* (*Cordyceps sinensis*) and *Tabllae bifendat* which were imported from China.

At first admission in August 1994, her consciousness was clear. There was slight jaundice in her eyes. The liver and spleen were enlarged, but no ascites was noted. There was palmar erythema in her hands and spider varices in her neck. The patient had arthritis in PIP joints but no rheumatoid nodules. Dipstick test showed negative for protein and occult blood.

Laboratory data showed an erythrocyte sedimentation rate (ESR) of 117 mm/h, total white blood cell count (WBC) of 1,500 /μl with 1% stabs, hemoglobin of 13.9 g/dl and platelet $5.9 \times 10^4$/μl. Electrolytes, blood urea nitrogen (BUN), and glucose were nor-

mal. The glutamyl transferase (GOT) was 40 (reference range 10-40) U/L, asparatate transferase (GPT) 26 (reference range 5-45) U/L, lactate dehydrogenase (LDH) 340 (reference range 120-240) U/L, alkaline phosphatase (ALP) 1,658 (reference range 100-280) U/L, lactate dehydrogenase (LAP) 508 (reference range 80-180) U/L, Ch-E 2,254 (reference range 3,000-7,000) mU/ml, and γ-glutamyl transpeptidase (γ-GPT) 515 (≦30) mU/ml. Serum total protein (TP) was 7.3 (reference range 6.7-8.3) g/dl with hypergammaglobulinemia (34.6%), albmin 2.9 (reference range 3.8-5.3) g/ml, total bilirubin (T-bil) 1.9 (reference range 0.2-1.1) mg/dl, and direct bilirubin (D-bil) 1.2 (reference range 0.0-0.5) mg/dl. Renal function was normal. Serum C reactive protein level (CRP) was 3.9 mg/dl. Rheumatoid factor was detected (positive by the latex agglutination method and RA particle aggulutination titer of 1: 160). Immunological tests revealed an antinuclear antibody titer of 1: 160 in which antimitochondrial antibody ($M_2$ IgM) was 19.8 U/ml and antismooth muscle antibodies were 40×. Anti-HBc antibody, anti-HBs antibody, HBV-DNA, HCV-RNA and IgM anti-HAV antibody were all negative. The prothrombin time was 11.0 (reference range 9.5-12.0) sec (65%) and activated partial thromboplastin time was 34.3 (reference range 23.5-42.5) sec (99%). Fibrinogen was 309 (reference range 155-415) mg/dl. There was no serological and microbiological evidence of viral and bacterial infection and allergies.

Radiography of chest and joints were normal. Ultrasound (Fig. 1A), CT scan (Fig. 1B) of abdomen and MRI showed marked deformity with multiple nodular lesions with scarred areas of liver without definite changes, potato liver, moderate splenomegaly and portal hypertension with splenorenal shunt. Endoscopic retrograde cholangiopancreatography demonstrated stenosis and obstruction of bile duct with choledochitis but there was no evidence of choledocholithiasis nor congenital abnormalities (Fig. 2). Choledochography also showed stenosis and obstruction of bile duct. The pictures were consistent with primary sclerosing cholangitis (PSC). Two liver biopsy specimens were taken on separate occasions. These revealed submassive hepatic necrosis, hepatic venous outflow obstruction and sinusoidal dilatation (Fig. 3). Bone marrow aspiration showed a mild hypercellular but normal myeloid-erythroid ratio and no excess of blasts.

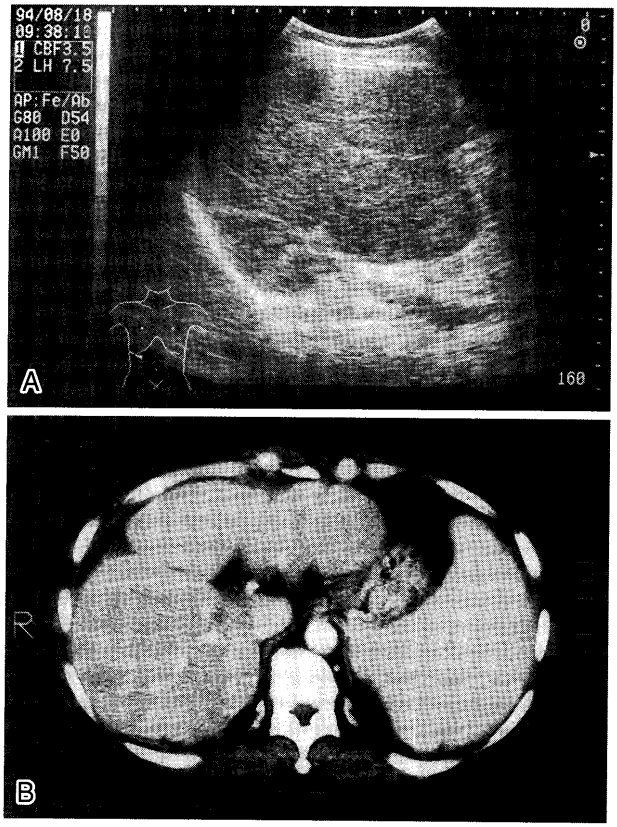


**Fig. 1** Ultrasound (A) and CT scan (B) of abdomen
Both ultrasound and CT scan show marked deformity with multiple nodular lesions with scarred areas of liver without definite changes, potato liver, moderate splenomegaly and portal hypertension with splenorenal shunt.

Finally, the patient was diagnosed as having AIH associated with VOD and PSC based on these observations. Since there was inflammation among the bilary duct and her bicytopenia worsened, intravenous methylpredonisolone (500 mg/day) for three consecutive days followed by predonisolone (50 mg/day) was initiated with ursodeoxycluic acid 900 mg. Her clinical features improved and she was discharged, taking predonisolone 30 mg/day. The patient was followed up at our out-patient clinic.

She was admitted to hospital several times before July 1997 since her clinical features flared. Upon the current admission, her consciousness score was 3 on the Glasgow Coma Scale. Physical examination

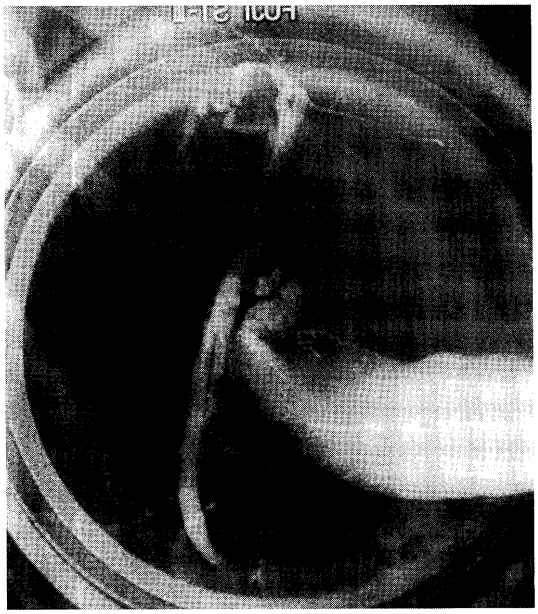

**Fig. 2** Endoscopic retrograde cholangiopancreatography
This demonstrates stenosis and obstruction of bile duct with choledochitis but there was no evidence of choledocholithiasis nor congenital abnormalities

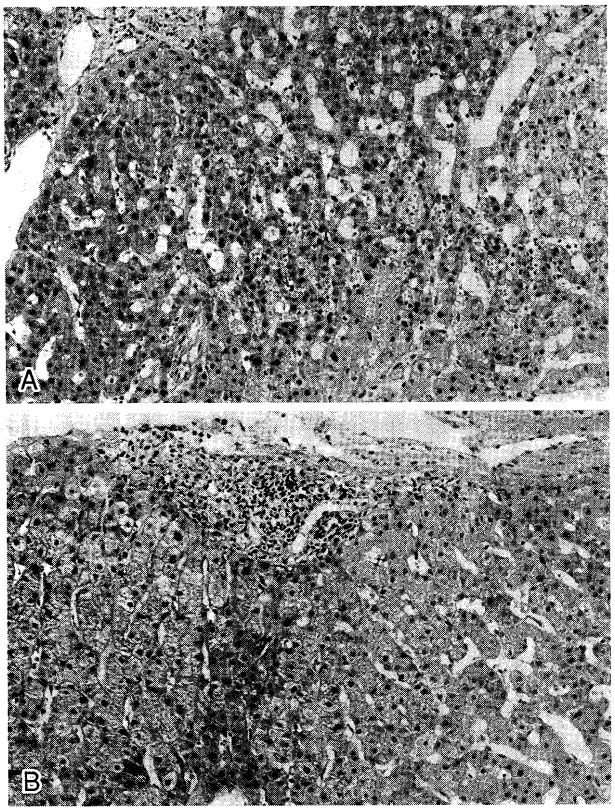


**Fig. 3** Liver biopsy
These reveal submassive hepatic necrosis, hepatic venous outflow obstruction and sinusoidal dilatation but not chronic non-suppurative destructive cholangitis.
A: The first time of biopsy, B: The second time of biopsy.

revealed a temparature of 37.8 ℃ and blood pressure of 110/74 mmHg. There was jaundice, slight ascites and peripheral edema. Dipstick test showed 2 + for bilirubin. Laboratory tests showed as follows : ESR 76 mm/h, WBC 19,400/μl, hemoglobin 12.4 g/dl, platelet $25.3 \times 10^4$/μl, CRP 20.5 mg/dl, serum creatinine level (Cr) 3.3 mg/dl, BUN 150 mg/dl and electrolytes within the normal limit. TP 5.9 g/dl, albumin 2.4 g/dl, T-bil 89 mg/dl, D-bil 7.5 mg/dl, AST 943 U/L, ALT 120 U/L, ALP 860 U/L, LDH 1,274 U/L, LAP 320 U/L, γ-GTP 241 U/L and $NH_3$ 98 (reference range 30-86) μg/ml. Based on these data, methylpredonisolone pulse therapy and $NH_3$ apheresis were performed. Her clinical features and data improved.

## Discussion

She was diagnosed as having AIH because 1) ANA and anti-smooth muscle antibody were positive, 2) IgG and transaminase were elevated, and 3) submassive hepatic necrosis was detected by liver biopsy. In addition, diagnosis of VOD of the liver was confirmed from findings of the second liver biopsy which showed hepatic venous outflow obstruction and sinusoidal dilatation. Moreover, endoscopic retrograde cholangiopancreatography revealed stenosis and obstraction of bile duct with choledochitis. Interestingly, during her clinical course, the pathogenesis of liver dysfunction changed.

Hepatic VOD is a progressive form of portal hypertension, characterised histologically by hepatic central vein dilatation and fibrosis, which is a potentially fatal cause of ascites and hepatic failure. The most common cause is exposure to plants that contain hepatotoxic pyrrolizidine, or endemic consumption of pyrrolizidine-containing plants and bush tea poisoning[1)~6)]. This patient had been taking Chinese teas, such as *Forfarae flos*, *cordyceps*, *Tabllae bifendat* and herb tea for 11 years before her liver dysfunction was pointed out. Although we could not detect pyrrolizidine in the tea which the patient had been taking, it might contribute to development of VOD[7)].

AIH and PSC are generally regarded as separate disease entities. Our case was diagnosed as AIH and VOD. In addition, clinical, laboratory and cho-

langiograhic findings also qualified her for the diagnosis of PSC. Gregorio et al[8] reported the overlap syndrome of PSC and AIH. We describe a patient with complicated autoimmune hepatic diseases including VOD. This case may provide an insight in understanding autoimmune hepatic diseases.

### References


1) **Carreras E, Granena A, Navasa M et al**: On the reliability of clinical criteria for the diagnosis of hepatic veno-occlusive disease. Ann Hematol **66**: 77–80, 1993
2) **Honneyer S, Teefey S, Jacobson A et al**: Veno-oclusive disease of the liver: prospective study of US evaluation. Radiology **184**: 683–686, 1922
3) **Liew C**: A comparative histopathological study of hepatic venous outflow obstraction in veno-occlusive disease and Budd-Chiari's syndrome. Chang Gung Med J **113**: 167–181, 1990
4) **Yeong ML, Swinburn B, Kennedy M et al**: Hepatic veno-occlusive disease associated with comfrey ingestion. J Gastroenterol Hepatol **5**: 211–214, 1990
5) **Ridker PM, McDermott WV**: Comfrey herb tea and hepatic veno-occlusive dsease. Lancet **25**: 657–658, 1989
6) **Bach N, Thung S, Schaffner F**: Comfrey herb tea induced hepatic veno-occlusive disease. Am J Med **87**: 97–99, 1989
7) **Buckley JA, Hutchins GM**: Association of hepatic veno-occlusive disease with the acquired immunodeficiency syndrome. Mod Pathol **8**: 398–401, 1995
8) **Gregorio GV, Portmann B, Karani J et al**: Overlap syndrome of primary sclerosing cholangitis and autoimmune hepatitis. Eur J Gastroenterol Hepatol **13**(2): 203–206, 2001
9) **Matsuishi E,Anzai K,Dohmen K et al**: Sonographic diagnosis of venoocclusive disease of the liver and danazol therapy for autoimmune thrombocytopenia in an autologous marrow transplant patient. Jpn J Clin Oncol **20**(2): 188–192, 1990
10) **Notsumata K, Ryorin H, Ohmizo R et al**: A case of non-cirrhotic portal hypertension with occluded central veins which is caused by pyrrolizidine alkaloid in an herb tea. Kanzo **29**(3): 394–399, 1988
11) **van Buuren HR, van Hoogstraten HJE, Terkivatan T et al**: High prevalence of autoimmune hepatitis among patients with primary sclerosing cholangitis. J Hepatol **33**(4): 543–548, 2000


## 細小肝静脈閉塞性疾患，原発性硬化性胆管炎を合併した自己免疫性肝炎の1例


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53歳の女性が肝障害で当科入院した．血液生化学検査，肝生検より自己免疫性肝炎，細小肝静脈閉塞性疾患の合併を認めた．さらに内視鏡的逆行性膵胆管造影で原発性硬化性胆管炎と診断した．プレドニゾロンとウルソデオキシコール酸により臨床所見ならびに検査所見は改善した．本症例は自己免疫性肝炎，細小肝静脈閉塞性疾患さらに原発性硬化性胆管炎と異なる3肝疾患の要素が見られた．何らかの免疫学的関与が疑われ，自己免疫性肝疾患の病態を考える上で貴重な症例と思われ報告する．