

Fibrosing Cholestatic Hepatitis C in a Patient with Systemic Lupus Erythematosus

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ABSTRACT

Fibrosing cholestatic hepatitis (FCH) is a rare form of liver injury characterized by aggressive clinical course and a propensity to liver failure. Almost all reported cases of FCH were associated with solid organ transplantation. We report a rare non-transplant patient with systemic lupus erythematosus and hepatitis C virus (HCV) infection, who developed FCH. The diagnosis was confirmed by histopathological examinations of the liver obtained at biopsy and autopsy, which were typical of FCH, including dense fibrosis, marked hepatocanicular cholestasis, ballooning of the hepatocytes, and relatively mild inflammation. In cases of FCH, extremely high viral loads were reported under excessive immunosuppressive status. Direct cytopathic effects of the HCV have been proposed to trigger the development of FCH. The patient was infected with HCV genotype 1a and had a moderate viral load. However, immunohistochemical staining revealed abundant deposition of HCV core protein around the periportal hepatocytes, where histological changes of FCH were noted. Immunohistochemical staining also showed activated hepatic stellate cells, suggesting underlying profibrogenic processes.

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Key words: Fibrosing cholestatic hepatitis; Hepatitis C virus;

HCV core protein; Hepatic stellate cell; Systemic lupus erythematosus

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INTRODUCTION

Fibrosing cholestatic hepatitis (FCH) was characterized by rapid and aggressive clinical course with marked jaundice and coagulopathy, whereas elevation of aminotransferase was relatively mild. The histopathologic changes of FCH are characterized by extensive periportal fibrosis and delicate fibrous septa extending into the sinusoidal spaces, ballooning of the hepatocytes, marked hepatocanicular cholestasis, ductular proliferation, and relatively mild inflammation^[1,2,3]. FCH was first described as a rare cholestatic variant of recurrent hepatitis B virus (HBV) infection in liver transplant recipients^[2,4,5]. Subsequently, it was reported to occur in hepatitis C virus (HCV)-associated transplant recipients^[6-10]. A recent retrospective unicenter study revealed that HCV-associated FCH (FCH-HCV) occurred in 1.8% of 918 patients with deceased donor liver transplant^[3].

FCH has not yet been reported in non-transplant patients, except for a case of concomitant infection with HCV and human immunodeficiency virus (HIV)^[11]. Before the introduction of combined antiretroviral therapy, rapidly progressive non-A, non-B hepatitis with jaundice was reported in HIV-infected elderly patients^[12]. A recent multicenter analysis of HCV-positive patients with diffuse large B-cell lymphoma suggested a high incidence of severe hepatic toxicity with significant increase in viral load during immunochemotherapy^[13]. However, whether these cases were of FCH or other hepatic injuries was not known because histopathological investigations were not performed. The mechanism underlying the occurrence and progression of FCH-HCV in non-transplant patients needs to be determined.

Herein, we report a rare case of a non-transplant patient with FCH-HCV that was complicated with systemic lupus erythematosus (SLE). Despite a moderate viral load, immunohistochemical staining revealed remarkable deposition of HCV core protein around the periportal hepatocytes. Immunohistochemical staining for alpha smooth muscle actin (α -SMA) showed activated hepatic stellate cells (HSCs), suggesting underlying profibrogenic processes. This case report emphasizes that FCH can occur in non-transplant patients, i.e., native livers.

CASE REPORT

A 70-year-old man was admitted to our hospital with a 1-week history of progressive fatigue. Laboratory tests showed marked jaundice. The serum total bilirubin was 10.8 mg/dL; direct bilirubin, 7.4 mg/dL; aspartate aminotransferase (AST), 201 IU/L; alanine aminotransferase (ALT), 241 IU/L; alkaline phosphatase (ALP), 402 IU/L (reference range, 115-359); gamma-glutamyltranspeptidase (γ GT), 609 IU/L; peripheral lymphocyte count, 378/ μ L; peripheral platelet count, 6.4×10^4 / μ L; and prothrombin time (PT), 69%. He had an 18-year history of chronic HCV infection and received conventional interferon (IFN)- α therapy at the age of 54, which was discontinued because of the development of adverse effect (details unknown). Later, his liver function was constantly tested by his family physician. Serum ALT levels were generally remained within 2 times the upper limit. Another medical condition- SLE was diagnosed at the Rheumatology department of our hospital 5 months before admission. Laboratory tests performed at that time revealed the following; serum total bilirubin, 0.9 mg/dL; direct bilirubin, 0.2 mg/dL; AST, 48 IU/L; ALT, 37 IU/L; ALP, 260 IU/L; γ GT, 39 IU/L; peripheral lymphocyte count, 476/ μ L; peripheral platelet count, 6.2×10^4 / μ L; PT, 76%; antinuclear antibody (ANA), 1:1280; anti-double strand DNA antibody (anti-dsDNA), 390.5 IU/mL (upper limit of normal, 20); and IgG, 3342 mg/dL. Abdominal computed tomography (CT) had revealed nodular deformity of the liver without ascites, which was consistent with compensated cirrhosis (Figure 1A). Administration of corticosteroid had stabilized the clinical course of SLE. However, recovery was complicated by pneumocystis pneumonia 3 months before the admission, and pentamidine isothionate inhalation and corticosteroid reduction was required. Liver function remained stable throughout the complication.

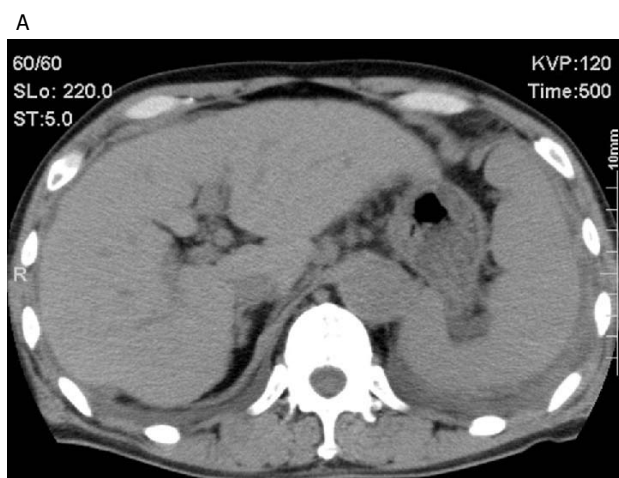


Figure 1 Abdominal computed tomography scan without contrast enhancement. A: The scan obtained at 5 months before admission, shows a cirrhotic liver without ascites. Bilateral pleural effusion is noted, which is indicative of pleuritis triggered by systemic lupus erythematosus; B: Scan obtained on admission shows a severe atrophic liver with massive ascites.

He did not drink alcohol or use illicit drugs. At the time of admission, his medications included prednisolone (20 mg/d), ursodeoxycholic acid (300 mg/d), and anti-fungal gargling liquid. There was no evidence of hypersensitivity reactions, including rash, fever, or peripheral eosinophilia. He was infected with HCV genotype 1a with a viral load of $5.7 \log_{10}$ IU/mL (approximately 5 million IU/mL). Tests for hepatitis A virus or HIV were negative. Positive anti-HBs was detected, however, both HBsAg and HBV-DNA were determined negative, indicating that there was no reactivation of HBV. Results of the tests for Epstein-Barr virus were consistent with past infection. Cytomegalovirus antigenemia was negative. ANA was 1:320; anti-dsDNA, 6.7 IU/mL; and IgG, 1210 mg/dL. Neither antimitochondrial antibody nor antismooth-muscle antibody were positive. CT revealed considerably different findings than those obtained 5 months previously; the liver was very atrophic with massive ascites, although all vasculatures were patent (Figure 1B). Magnetic resonance imaging cholangiography showed no evidence of concurrent biliary problems. Trans-jugular liver biopsy was performed. Histological examination showed hepatocytes swelling and hepatocanicular cholestasis. Fibrosis occasionally extended into the sinusoidal spaces and enclosed hepatocytes, mainly around the periportal areas. Lymphocytic infiltration was mild (Figure 2). Although HCV-related hepatic injury was suspected, IFN therapy was not warranted or was relatively contraindicated for this patient, because of its potentially stimulatory effects on autoimmunities^[14-16]. Despite administration of albumin, fresh frozen plasma, lactulose, and diuretics, as well as corticosteroid reduction, the patient's condition continued to deteriorate, and he developed hepatic coma. He died 6 weeks after the admission. Just before death, his serum total bilirubin was 18.9 mg/dL; direct bilirubin, 12.8 mg/dL; AST, 114 IU/L; ALT, 128 IU/L; ALP, 318 IU/L; γ GT, 68 IU/L; peripheral lymphocyte count, 92/ μ L; peripheral platelet count, 1.9×10^4 / μ L; and PT, 38 %.

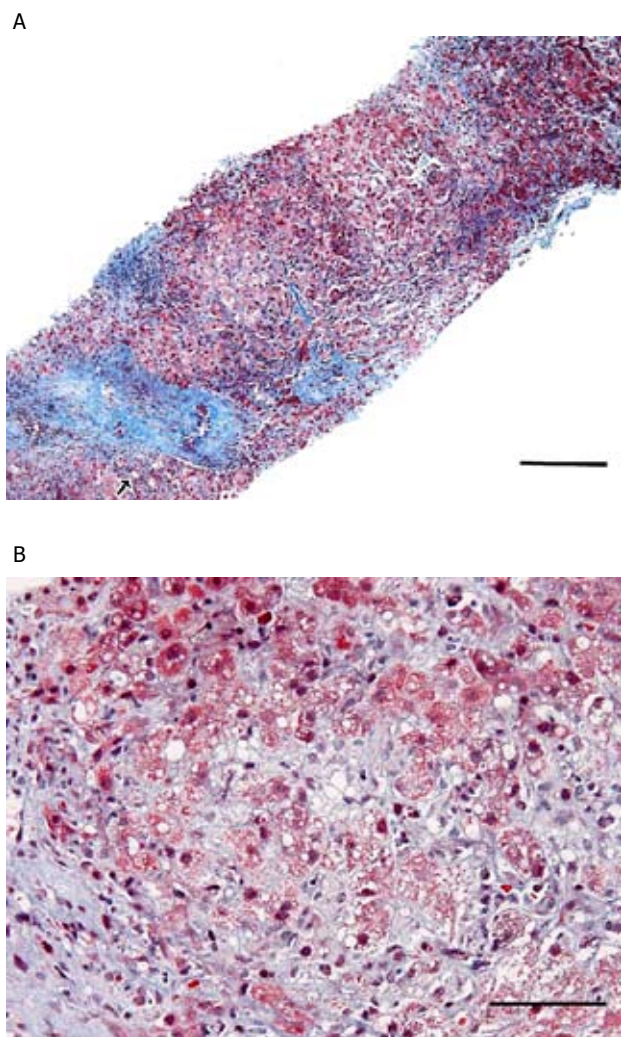


Figure 2 Histological examination of the trans-jugular liver biopsy specimen. The specimen was obtained 3 weeks before the death of the patient. A: Delicate fibrous septa occasionally encloses the hepatic sinusoidal spaces. Conspicuous ballooning of the hepatocytes is observed. Inter-lobular bile ductules are intact (arrow); B: Under high magnification, ballooning of the hepatocytes and hepatocanalicular cholestasis are apparent. Lymphocytic infiltration is mild. A: Masson-Trichrome staining; B: Hematoxylin-eosin staining. Scale bar, 200 μ m in A, and 50 μ m in B.

An autopsy was performed. Exploration of the abdomen revealed 1600 mL of serous non-bloody ascites. The liver had shrunk notably (weight, 500 g), and become grossly micro-nodular cirrhotic with dark greenish appearance because of the marked cholestasis. Hepatobiliary obstruction was absent, and all hepatic vasculatures were patent. Microscopically, the hepatocytes showed conspicuous ballooning degeneration and cholestasis with feathery degeneration (Figure 3A). Ductular proliferations were also observed. Trichrome staining showed dense periportal and pericellular fibrosis (Figure 3B). Fibrous capsules surrounding the hepatic nodules excluded the possibility of nodular regenerative hyperplasia, which was associated with SLE and mimicked cirrhosis^[17]. The distinct histopathological features, peculiar biochemical profile of marked bilirubinemia with moderate elevation of serum ALT, immunocompromised status, and absence of any other causes to account for the liver failure led to the final diagnosis of FCH-HCV, at the completion of the autopsy.

DISCUSSION

Unlike the involvement of immunologically mediated injuries in

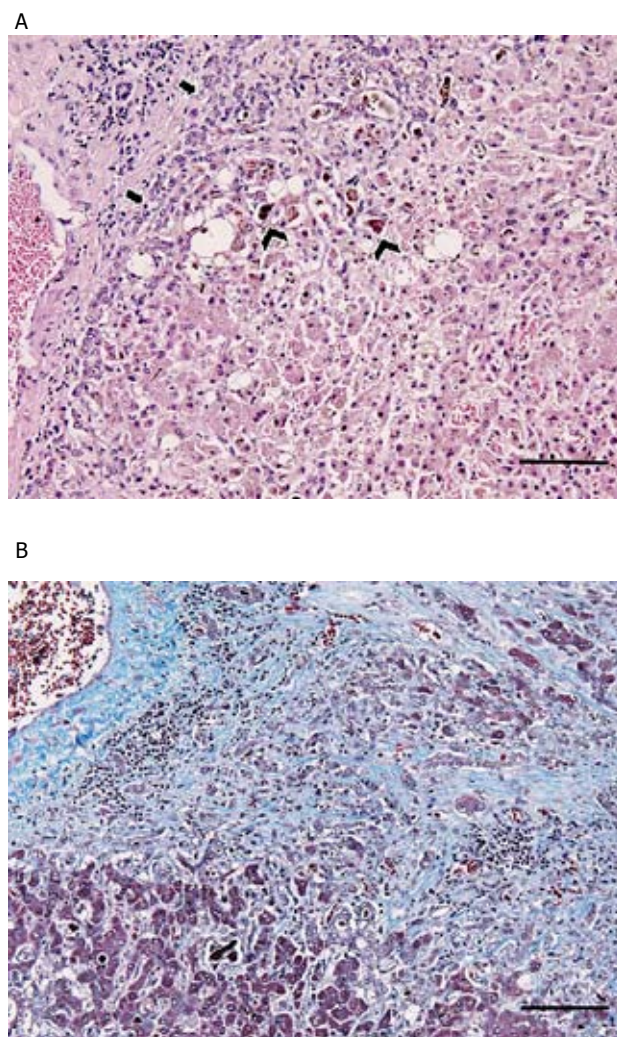


Figure 3 Histological examination of the liver obtained at autopsy. A: Confluent necrosis of the hepatocytes. Cholestasis is observed and bile plugs are visible (arrow-head). Ductular proliferations are identified (arrow). Inflammatory changes are scarce; B: Extensive periportal fibrosis. Fibrous septa extending into the sinusoids and enclosing hepatocytes is noted; this finding is consistent with pericellular fibrosis. The histological finding at autopsy is consistent with that obtained at biopsy, but dense diffuse fibrosis is apparent in the autopsy specimen. A: Hematoxylin-eosin staining; B: Masson-Trichrome staining. Scale bar, 100 μ m.

non-cholestatic hepatitis B or C, the pathogenesis of FCH involves the direct cytopathic effects of the viruses^[6,7,18]. Uninhibited viral replication in hepatocytes has been considered to trigger the development of FCH under excessive immunosuppressed conditions such as organ transplantation, corticosteroid or cytotoxic agent administration, and coinfection with HIV. The viral loads in patients with FCH-HCV were reported to be extremely high (mean viral load, 14.4 million IU/mL)^[3]. However, FCH-HCV may not always be associated with an increase in viremia^[11,19,20], as in our patient. HCV may remain concentrated within the secretory apparatus of the hepatocytes, and the intrahepatic viral replication might not be accurately reflected by the viremia level^[10]. Circulating viral load may fluctuate during the time of evaluation^[21], and severely damaged tissues may not be able to support high-level replication of the virus, resulting in lower viral loads^[22]. In our study, viral distribution in the liver tissue was measured by immunohistochemical staining for the HCV core protein (Figure 4). The core-positive granules were abundant particularly near the periportal areas where FCH-related histopathological changes were

remarkable. This finding suggests a possible adverse effect of HCV proteins on hepatocytes. An alternative hypothesis suggests that enhanced divergence of HCV quasispecies might influence disease progression to FCH-HCV^[23,24].

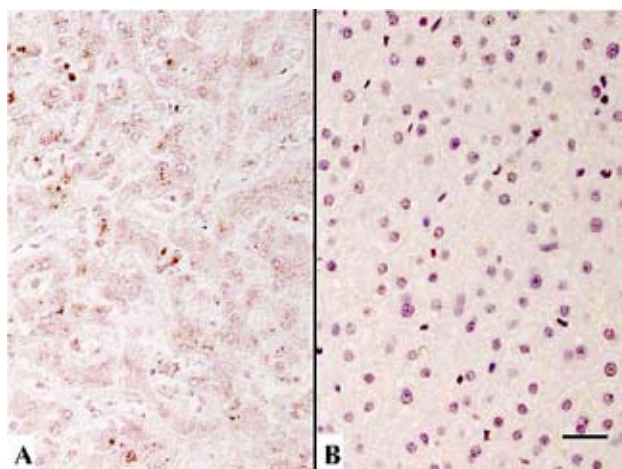


Figure 4 Immunohistochemical staining for cp9, the hepatitis C virus (HCV) core protein. A, Autopsy liver specimen: core-positive granules are abundant in the hepatocytes mainly around the periportal areas. Brown granules represent HCV core proteins stained for anti-cp9. B, Control liver: This was obtained from an unaffected area of the resected liver of a patient with hepatocellular carcinoma and chronic hepatitis B virus infection. Scale bar, 50 μ m.

Not only excessive immunosuppression but also inappropriate immune-profiles may be relevant to uncontrollable viral replication. The intrahepatic immune-profile typically shows a tendency toward the T helper cell subtype 2 (TH2)-predominance in FCH-HCV, unlike TH1-predominance in conventional HCV recurrence^[25,26]. The TH2 immune response may favor viral replication and cause graft damage. Patients with minimal histologic recurrence after HCV-related liver transplantation show vigorous HCV-specific CD4+ T-cell responses, whereas patients with progressive HCV recurrence show a decline in these effector responses^[27].

SLE-derived immunological deficits, such as inefficient control of viral infections, might have modified the sequel of HCV infection in our patient^[16,28,29]. Moreover, aging seems to be a likely cofactor; hepatocytes transplanted from older donors might show a reduced proliferative response and lead to profound apoptosis^[3,30]. All these factors, i.e., corticosteroid therapy, SLE-derived immunological deficits, aging, and cirrhosis might contribute to "the net state of immunosuppression"^[31], resulting in an inability to efficiently combat HCV infection.

Hepatotoxic effects of drugs should also be taken into account. Azathioprine is known to induce liver injury characterized by cholestasis and perisinusoidal fibrosis^[32]. Idiosyncratic drug-toxicity could not be completely ruled out; however, drug-induced hepatotoxicity was unlikely in our patient because of the paucity of the prescribed drugs, absence of hypersensitivity-type clinical symptoms, and lack of characteristic histopathological findings such as eosinophilic infiltrations and granuloma development.

Unfortunately, the outcome of FCH is extremely poor. Attempts of re-transplantation are unsuccessful in most cases^[33,34]. The appropriate treatment of FCH depends on accurate detection of this condition at an earlier stage^[35]. At present, no reliable markers for FCH are available, and diagnosis is mostly made on the basis of histological examinations of the liver. The early activation of HSCs can be a predictor of the subsequent development of

profound fibrosis^[36,41]. HSC activity was measured by α -SMA immunostaining of the autopsy specimen (Figure 5). Dark brown granules were found particularly near the periportal areas, indicating activation of HSCs. These findings along with conventional histological examinations might be used to predict the development of FCH.

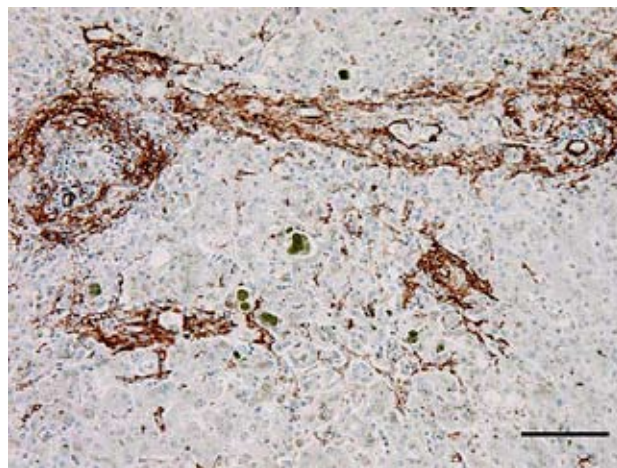


Figure 5 Alpha smooth muscle actin (α -SMA) immunostaining of the autopsy liver specimen. Brown granules represent areas stained for α -SMA. Scale bar, 100 μ m.

In cases of HBV-associated FCH, the accumulation of HBV surface antigen within the endoplasmic reticulum and Golgi complex has been postulated to lead to stress of these organelles, resulting in hepatocytic death^[10,37]. In FCH-HCV, the HCV core proteins may alter mitochondrial function and produce oxidative stress^[38,39]. Direct interaction between HCV proteins and HSCs may contribute to HCV-induced liver fibrosis^[40-43]. Antiviral therapy may improve the outcomes of the patients, if the direct cytopathic effects of the viruses' are responsible for the development of FCH. IFN- α therapy has been found to be effective in FCH-HCV patients^[19]. However, both response and tolerability to IFN therapy are not always favorable^[18,44,45]. Interestingly, improvement in FCH-HCV was observed after cessation of pegylated IFN and ribavirin therapy, despite viremic relapse with non-cholestatic hepatitis^[46]. Reduction in immunosuppression might have a beneficial effect on the liver in renal transplant recipients with FCH-HCV^[47]. In such cases, immune response to HCV antigens seems to be reconstituted, together with the achievement of optimal balance between immunosuppression and augmentation. Switching of the immune response toward a more TH1-like response, i.e., suppression of viral replication, might also be a useful strategy^[24]. Resuscitation of the immune-profiles, and administration of efficient antiviral therapies might help in controlling the progression to FCH^[3,26].

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