A histologically proven case of progressive liver sarcoidosis with variceal rupture

Hitoshi Yoshiji, Kou Kitagawa, Ryuichi Noguchi, Masahito Uemura, Yasuhide Ikenaka, Yosuke Aihara, Keisuke Nakanishi, Yusaku Shirai, Chie Morioka, Hiroshi Fukui

Hitoshi Yoshiji, Kou Kitagawa, Ryuichi Noguchi, Masahito Uemura, Yasuhide Ikenaka, Yosuke Aihara, Keisuke Nakanishi, Yusaku Shirai, Chie Morioka, Hiroshi Fukui, Third Department of Internal Medicine, Nara Medical University, Kashihara, Nara 634-8522, Japan

Author contributions: Yoshiji H and Kitagawa K described the clinical case, obtained informed consent from the patient, conceived the study, participated in its design, assisted in data collection, coordinated and helped draft the manuscript; Yoshiji H undertook the literature research and contributed to the writing; Uemura M, Ikenaka Y, Noguchi R, Shirai Y, Aihara Y, Nakanishi K, Morioka C and Fukui H were responsible for the diagnosis, patient management and review.

Correspondence to: Hitoshi Yoshiji, MD, PhD, Third Department of Internal Medicine, Nara Medical University, Shijo-cho 840, Kashihara, Nara 634-8522, Japan. yoshijih@naramed-u.ac.jp

Telephone: +81-744-223051 Fax: +81-744-247122

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Abstract

Sarcoidosis is a chronic multi-systemic granulomatous disease, and liver involvement frequently occurs. In most cases, no evidence of liver dysfunction is observed, and portal hypertension due to sarcoid liver diseases is a rare occurrence. Moreover, no case of liver sarcoidosis has ever been reported with confirmation of the disease progression. Herein we describe a patient having hepatic sarcoidosis with severe portal hypertension and liver dysfunction. The diagnosis was histologically confirmed from granulomatous status to established liver cirrhosis over 10 years. A 46-year-old woman developed massive hematemesis due to the rupture of gastric cardial varices. She underwent emergency endoscopic injection sclerotherapy, and clear evidence of chronic hepatic failure. Twelve years ago, she was diagnosed as having sarcoidosis with respiratory clinical symptoms. Liver biopsy revealed asymptomatic incidental granulomas without fibrosis development. After a couple of years, features of liver dysfunction were manifest and progressed. Ten years after the first biopsy, a second liver biopsy was performed, and well-established dense fibrosis was revealed. Although significant liver dysfunction with portal hypertension is rarely seen in sarcoidosis, this case indicates that we have to consider the possibility that sarcoidosis may cause end-stage liver cirrhosis.

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Key words: Liver sarcoidosis; Portal hypertension; Hepatic failure; Liver cirrhosis

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INTRODUCTION

Sarcoidosis is a systemic disease of unknown etiology related to exaggerated cellular immunological reactions, and is characterized by multiple occurrences of non-caseating epithelioid granulomas in several organs, among which the liver is the most frequently affected [1-3]. In the majority of cases, liver dysfunction is usually mild and transient, and the condition is clinically silent. The diag-
nosis of liver sarcoidosis is difficult, because symptoms or functional derangement due to the involvement of the liver are uncommon in sarcoidosis. Only a few such patients have exhibited progressive clinical features such as portal hypertension. Liver cirrhosis and variceal bleeding develop in less than 1% of these cases but can be life-threatening complications of hepatic sarcoidosis. To date, the progression of liver sarcoidosis could be followed up in only a few cases. Herein we report a case in which histological examination successfully confirmed the progression of liver sarcoidosis from granulomatous status without fibrosis development, to established liver cirrhosis with dense fibrosis septa over a period of 10 years. The patient had severe clinical manifestations, chronic hepatic failure and variceal rupture.

CASE REPORT

A 46-year-old woman developed massive hematemesis and was admitted to our hospital. Emergency endoscopic examination revealed active bleeding from gastric cardial variceal rupture (Figure 1A). She underwent emergency endoscopic injection sclerotherapy (EIS) (Figure 1B). She had several clinical manifestations of decompensated liver cirrhosis, such as ascites. The laboratory data on admission showed severe liver dysfunction (Table 1). The etiology of the chronic hepatic failure was not clear from the laboratory data since the hepatitis virus markers including hepatitis B and hepatitis C were all negative, and immunological tests, such as anti-nuclear antibody and anti-mitochondrial antibody were negative as well. Twelve years ago, she had been diagnosed as having sarcoidosis with respiratory clinical manifestations. At the time, she was treated with steroid therapy, the respiratory manifestations improved, and finally, after 2 years treatment, the steroid could be tapered off. At that time, the liver biopsy revealed non-caseating granulomas in the liver without fibrosis development. Aggregates of epithelioid histiocytes and Langhans-type giant cells were observed, surrounded by lymphocytes (Figure 2A). Enhanced computed tomography (CT) showed multiple low-attenuation areas up to 10 mm in diameter, indicating multiple granulomas in the liver. There was no splenomegaly at this time (Figure 2B). Although the steroid therapy achieved some improvement of the respiratory symptoms, liver dysfunction in this patient persisted. Since the liver dysfunction had progressed [alanine aminotransferase/aspartate aminotransferase 68/75 IU/L, alkaline phosphatase (ALP) 813 IU/L, T-Bil 21 mg/dL] a second liver biopsy was performed, 10 years after the first biopsy. The second biopsy revealed pseudo-lobular dense fibrosis with persistent moderate infiltration (Figure 3A). The CT findings significantly changed as well. Enhanced CT scanning at the second biopsy showed a marked splenomegaly, and the surface of the liver was irregular, indicating portal hypertension and liver cirrhosis, respectively (Figure 3B). After a couple of sessions of EIS and interventional therapy, endoscopic findings of the varices alleviated.

| Table 1  The Laboratory data on admission |
|-----------------------------------------|
| Items tested                          | Results         |
| Blood cell count                      | Patient         | Normal         |
| WBC (/µL)                             | 3200            | 3900-9800      |
| RBC (x 10¹²/µL)                       | 256             | 427-570        |
| Hb (g/dL)                             | 9.0             | 13.5-17.6      |
| Plt (x 10¹²/µL)                       | 8.6             | 13.1-36.2      |
| Coagulation function                 | PT (s)          | 18.7           | 10-15          |
| Viral examination                     | HBsAg           | (-)            | (-)            |
|                                      | HBV-DNA         | (-)            | (-)            |
|                                      | HCV Ab          | (-)            | (-)            |
| Biochemical parameters                | CRP (mg/dL)     | 0.6            | <0.2           |
|                                      | TP (g/dL)       | 7.2            | 6.4-8.1        |
|                                      | Alb (g/dL)      | 3.4            | 4.0-5.1        |
|                                      | ZTT (KU)        | 21.5           | 3-13           |
|                                      | AMY (IU/L)      | 72             | 40-200         |
|                                      | AST (IU/L)      | 70             | 12-32          |
|                                      | ALT (IU/L)      | 36             | 5-36           |
|                                      | ALP (IU/L)      | 225            | 116-250        |
|                                      | γ-GTP (IU/L)    | 924            | 115-359        |
|                                      | γ-glutamyltransfesrase | 145        | 11-69          |
|                                      | ChE (IU/L)      | 98             | 192-446        |
|                                      | TG (mg/dL)      | 36             | 30-150         |
|                                      | T-Ch (mg/dL)    | 125            | 120-240        |
|                                      | BUN (mg/dL)     | 34             | 8-20           |
|                                      | CRE (mg/dL)     | 0.75           | 0.53-1.01      |
|                                      | Na (mEq/L)      | 137            | 137-146        |
|                                      | K (mEq/L)       | 4.8            | 3.6-4.8        |
|                                      | T-Bil (mg/dL)   | 4.8            | 0.3-1.1        |
|                                      | NH3 (µg/dL)     | 145.7          | 12-66          |
|                                      | ACE (IU/L)      | 17.5           | 8.3-21.4       |
|                                      | FBS (mg/dL)     | 85             | 60-100         |
|                                      | HbAic (%)       | 4.10           | 4.3-5.8        |
|                                      | Fe (µg/L)       | 37.7           | 3.6-114        |

DISCUSSION

In this case, we observed that the liver sarcoidosis progressed from the granulomatous status without fibrosis to established liver cirrhosis associated with severe portal hypertension and hepatic failure. Portal hypertension is an uncommon finding in sarcoidosis, and the mechanisms involved are not completely understood. Several reports have suggested that hepatic granulomas may play an important role under certain conditions. Granulomas are the main histological features of sarcoidosis. The granulomatous lesions in hepatic sarcoidosis are usually very small and asymptomatic. However, in a few cases, chronic intrahepatic cholestasis may develop. Intrahepatic cholestasis has been reportedly detected in up to half of...
the biopsy specimens. Cholestasis may result from hepatic granulomas, or involvement of the intra- or extrahepatic biliary tract by sarcoid, or compression of the common bile duct by enlarged peri-hilar lymph nodes. Chronic cholestasis and the possible coexistence of other liver-damaging diseases have been suggested as causes of the liver cirrhosis and portal hypertension. However, this was not the case in our patient, since the liver biopsy revealed no intrahepatic cholestasis (ALP 148 IU/L, γ-guanosine triphosphate 68 IU/L, T-Bil 11 mg/dL). Furthermore, the granulomatous cholangitis which represent vanishing bile ducts was not observed either.

Alternatively, portal hypertension in liver sarcoidosis may be attributed to obstruction of the portal flow, be-

Figure 1  Endoscopic examination at the time of cardial variceal rupture. A: Endoscopic examination revealed active bleeding consequent to gastric cardial variceal rupture. B: Fluoroscopic image of emergency endoscopic injection sclerotherapy with 5% ethanolamine oleate with iopamidol.

Figure 2  First histological examination of the liver, and the image of enhanced computed tomogram. A: The first liver biopsy showed non-caseating granulomas in the liver without fibrosis development. Aggregates of epithelioid histiocytes and Langhans-type giant cells were observed surrounded by lymphocytes. The original magnifications are × 40 and × 200, respectively. B: Enhanced computed tomogram showing multiple low-attenuation areas up to 10 mm in diameter, indicating multiple granulomas in the liver (white arrows). There was no splenomegaly at this time.

Figure 3  Second histological examination of the liver, and the image enhanced computed tomogram. A: The second biopsy revealed pseudo-lobular dense fibrosis with moderate infiltrating cells; B: The images of the enhanced computed tomography (CT) were significantly altered, too. The enhanced CT at the second biopsy showed a marked splenomegaly, and the surface of the liver was irregular, indicating portal hypertension and liver cirrhosis, respectively.

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cause of granulomas in the portal area causing a pre-sinusoidal block. A granulomatous phlebitis obstructing the portal and hepatic veins may lead to ischemia and parenchymal extinction\[6,7\].Portal vein thrombosis sometimes happens in liver sarcoidosis perhaps because of stasis consequent to the obliteration of small portal veins. Budd-Chiari syndrome may also develop because of extrinsic compression of the hepatic veins by sarcoid granulomas, causing narrowing of the veins, venous stasis, and subsequent thrombosis\[6,7\]. In these cases, most of the patients develop portal hypertension not associated with liver cirrhosis. The second biopsy in our patient demonstrated a pseudo-lobular fibrotic septa and cirrhosis, and the laboratory data were in compliance with the histological findings, indicating that deregulation of these vessels was not the trigger of portal hypertension in our patient. In the CT image, no severe stricture such as hepatic vein and/or inferior vena cava (data not shown) could be observed. However, there is a limitation in this patient, since we did not measure the HVPG by hepatic venography.

In general, corticosteroids are employed for treatment of sarcoidosis when organ function is threatened, although the role of corticosteroids in the treatment of hepatic sarcoidosis is unclear\[8,9\]. Although these drugs improve lung function, their effects on hepatic sarcoidosis are difficult to assess. Our patient was first diagnosed as having lung sarcoidosis and received corticosteroid therapy\[8\]. The respiratory clinical manifestations were improved by administration of corticosteroids, but then the liver dysfunction started. It has been reported that corticosteroids may improve the results of liver function tests in those with mild to moderate abnormalities\[5,6\], but without any consistent clinical or pathologic effects in those with severe disturbances\[6,7\]. In spite of the biochemical improvement, the liver biopsy may show progression of the disease\[8\]. In our patient, her second biopsy showed significant progression even though the respiratory clinical manifestations improved. Treatment of hepatic sarcoidosis with corticosteroids tends to reduce the liver size and the number of hepatic granulomas\[12\], but does not alleviate portal hypertension\[11,13,14\]. Although the exact mechanisms were not clear at this time, corticosteroid treatment may have been involved in the progression of hepatic sarcoidosis in this case. Accumulation of cases of hepatic sarcoidosis with disease progression would be required to elucidate the mechanistic insights in the future.

In conclusion, we herein report the first case of hepatic sarcoidosis with severe portal hypertension and liver dysfunction. The diagnosis was histologically confirmed from the granulomatous status, progressing to established liver cirrhosis over 10 years. Although significant liver dysfunction with portal hypertension is rarely seen in sarcoidosis, we have to consider the possibility that sarcoidosis may cause end-stage liver cirrhosis.

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