

# Hepatic Sarcoidosis in a Patient with Chronic Hepatitis B Virus Infection

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Sarcoidosis is a systemic inflammatory granulomatous disease affecting multiple organs, including liver, spleen, heart, eyes, and skin. Liver involvement is reported in 11.5% of cases and many studies have reported on the association between hepatitis C virus infection and sarcoidosis. However, the role of hepatitis B virus (HBV) infection as a trigger for sarcoidosis has never been reported. We describe a case of hepatic sarcoidosis in a patient with chronic hepatitis B infection, with a possible link between the two. It is the first case report of a patient with interferon- $\alpha$ -naïve chronic HBV infection presenting with hepatic sarcoidosis accompanied by portal hypertension and liver cirrhosis. (*J Rheum Dis* 2015;22:200-204)

**Key Words.** Sarcoidosis, Hepatitis B virus, Liver cirrhosis, Portal hypertension

## INTRODUCTION

Sarcoidosis is an autoimmune disease which is characterized by systemic non-caseating granuloma in multiple organs [1,2]. It has been reported to be able to occur in every race and age, and the incidence ranges 1 to 40 cases per 100,000 persons worldwide [2]. However, the incidence of sarcoidosis in Asian is less than that of Caucasian: 1 to 2 cases per 100,000 in Japan and 0.13 cases per 100,000 in Korea [3,4]. Although sarcoidosis can be suspected when patients present disease-related clinical and radiologic features, typical histologic findings are essential to make a diagnosis [5].

Sarcoidosis commonly involves lungs and lymph nodes up to 90% and it can also affect almost all organs including liver, spleen, heart, eyes and skin [2]. Liver involvement can be found in 11.5% of the cases [6], and it is usually asymptomatic. Only 5% to 30% patients experience atypical symptoms such as nausea, vomiting and abdominal pain [7]. The progressive complication like liver cir-

rhosis is rarely presented at a rate less than 1% [2].

There have been several reports regarding the association between hepatitis C virus (HCV) and hepatic sarcoidosis. Interferon- $\alpha$  (INF- $\alpha$ ), which was used to treat HCV, was first considered to induce hepatic sarcoidosis. And then there were accumulating reports that HCV itself can be an initiating factor for hepatic sarcoidosis [8]. However the association between the development of sarcoidosis and hepatitis B virus (HBV) was not clarified and there was no case report on sarcoidosis in patients with chronic HBV infection who were not treated by INF- $\alpha$ . Hence, we first describe a patient with INF- $\alpha$ -naïve chronic HBV infection presenting hepatic sarcoidosis accompanied by portal hypertension and liver cirrhosis.

## CASE REPORT

A 49-year-old woman with chronic HBV infection was referred to our hospital for loss of appetite and mild

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ab.dominal bloating and discomfort. She was diagnosed with HBV infection 10 years ago, but she has been on regular check-ups without the treatment for chronic HBV infection so far. It was assumed that she had been infected with HBV by perinatal transmission as her mother and siblings had also been diagnosed with HBV infection. Other than B-viral hepatitis, she had no medical history.

**Table 1.** Laboratory data

Variable	Patient's result	Reference range
White cell count (/ $\mu$ L)	2,940	4,000 ~ 10,800
Hemoglobin (g/dL)	11.8	12.0 ~ 16.0
Platelet count (/ $\mu$ L)	119,000	150,000 ~ 400,000
Prothrombin time (s)	12.10	9.2 ~ 12.3
ESR (mm/h)	12.0	0.0 ~ 20.0
AST (IU/L)	44	13.0 ~ 34.0
ALT (IU/L)	22	5.0 ~ 46.0
Total protein (g/dL)	8.7	6.0 ~ 8.0
Albumin (g/dL)	3.2	3.3 ~ 5.3
Total bilirubin (mg/dL)	0.7	0.4 ~ 1.5
Gamma-GT (IU/L)	175	7.0 ~ 35.0
LDH (IU/L)	277	119 ~ 247
ALP (IU/L)	296	32 ~ 93
HBs Ag	Positive	Negative
HBe Ag	Negative	Negative
Anti HBe	Positive	Negative
HBV-RQ PCR (IU/mL)	60.3	< 20
Anti HCV	Negative	Negative

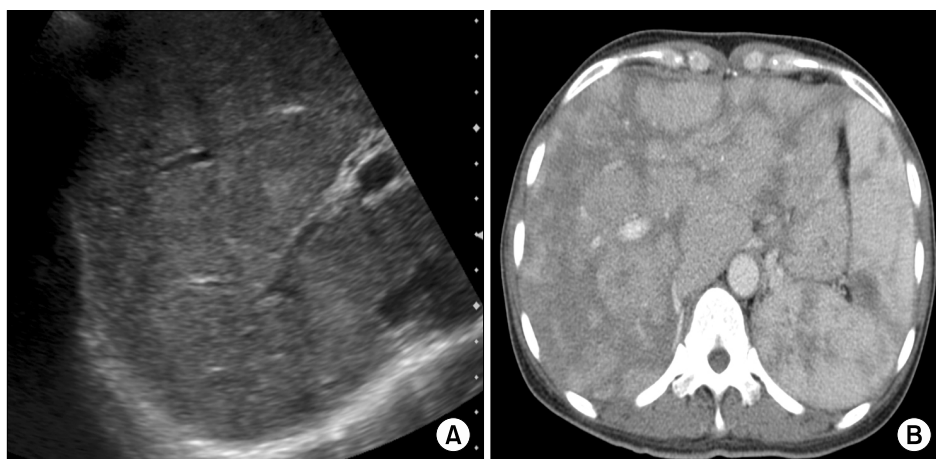
Ag: antigen, ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase, ESR: erythrocyte sedimentation rate, GT: glutamyl transpeptidase, HBe: hepatitis B e, HBs: hepatitis B surface, HBV: hepatitis B virus, HCV: hepatitis C virus, LDH: lactate dehydrogenase, RQ PCR: real-time quantitative polymerase chain reaction.

Physical examination revealed mild tenderness on right upper quadrant area of abdomen without rigidity. Liver was slightly palpated below the margin of right rib. Laboratory results are shown in Table 1.

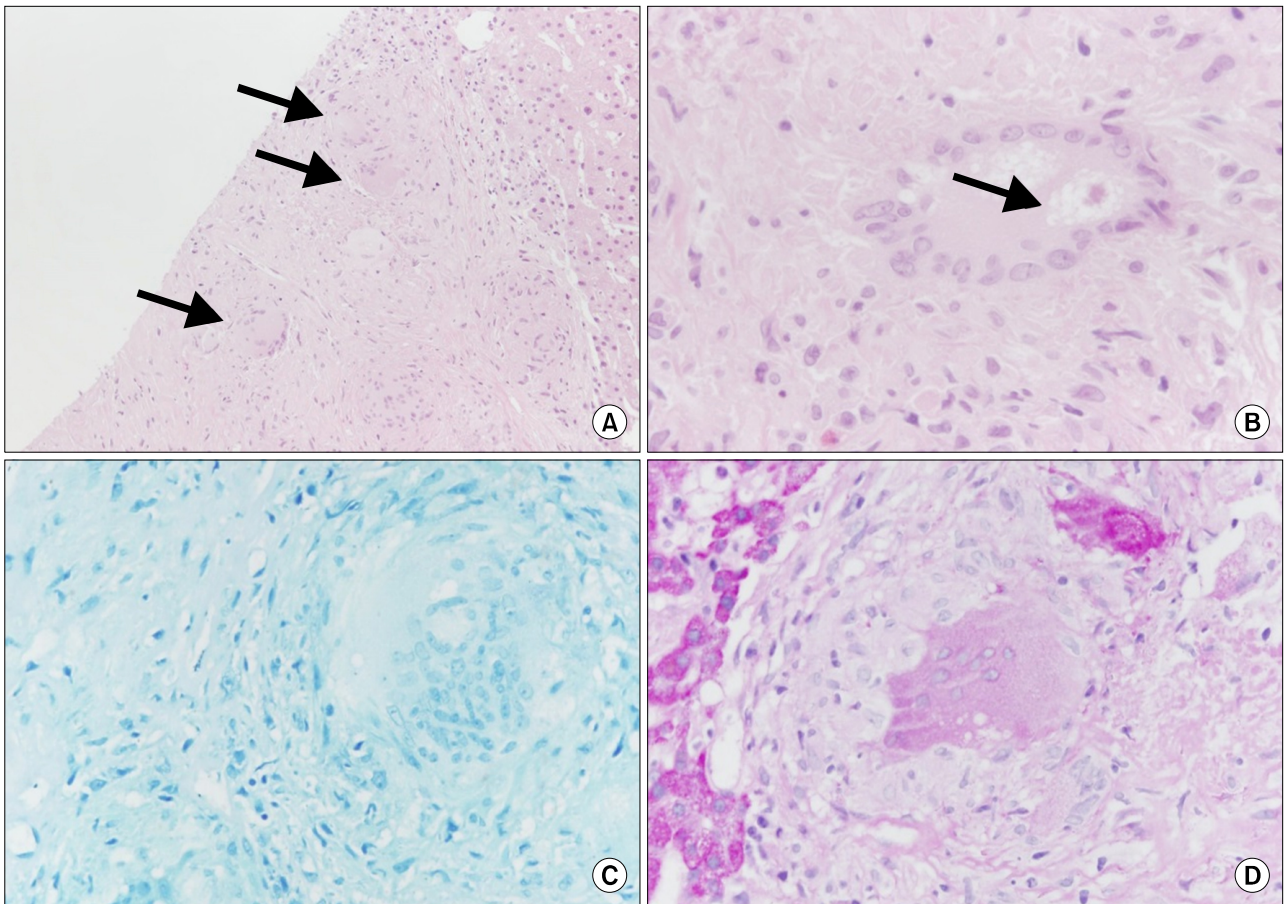
The abdomen sonogram showed that parenchymal echogenicity of the liver was coarse without space occupying lesion and the spleen was enlarged upto 12.63 cm (Figure 1A). Abdomen computed tomography (CT) scan revealed hepatosplenomegaly with heterogeneous enhancement and multiple lymph node enlargements around aorto-caval, para-aortic and peri-pancreatic space (Figure 1B). Liver stiffness measurement by transient elastography (Fibroscan<sup>®</sup>; Echosens, Paris, France) was 24.2 kPa which is compatible with liver fibrosis at stage 4. The esophagogastroduodenoscopy was also done and it showed esophageal varix (small straight esophageal varix, F1), which is a clinical complication of portal hypertension.

Although she had been stable with chronic hepatitis B infection and lab findings were within normal range, the CT scan showed hepatosplenomegaly and multiple lymph node enlargements. Therefore, liver biopsy was needed to exclude other causes. Histology finding revealed chronic granulomatous inflammation showing multifocal multinucleated giant cells (Figure 2A). It did not show any necrosis in the granuloma, so sarcoidosis and drug reaction could be suspected. However, we could conclude the histology finding as a sarcoidosis because asteroid bodies were noted (Figure 2B). Acid fast bacilli stain and periodic acid Schiff stain were negative, therefore the possibility of mycobacterial infection or fungal infection was low (Figure 2C and 2D).

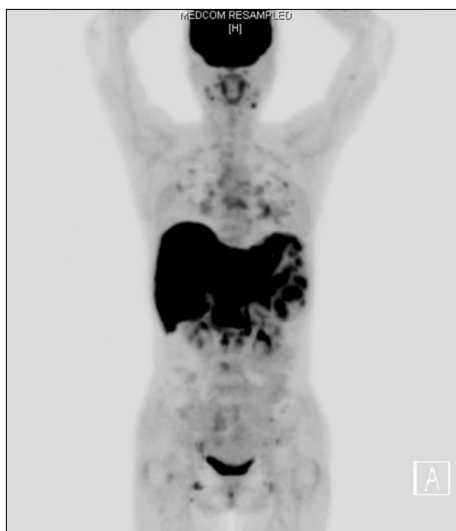
Positron emission tomography (PET) scan was also done and it showed numerous hyper-metabolic foci in the



**Figure 1.** Abdomen sonogram (A) and abdomen computed tomography (CT) scan (B). Sonogram (A) reveals coarse parenchymal echogenicity of the liver. CT scan (B) shows heterogeneous enhancement in the enlarged liver and the spleen.



**Figure 2.** Liver biopsy showing the non-caseating granuloma (arrows) (A) and asteroid body (B). Special staining for acid fast bacilli (AFB) (C) and periodic acid Schiff (PAS) (D) were negative (A: H&E,  $\times 100$ ; B: H&E,  $\times 400$ ; C: AFB,  $\times 400$ ; D: PAS,  $\times 400$ ).

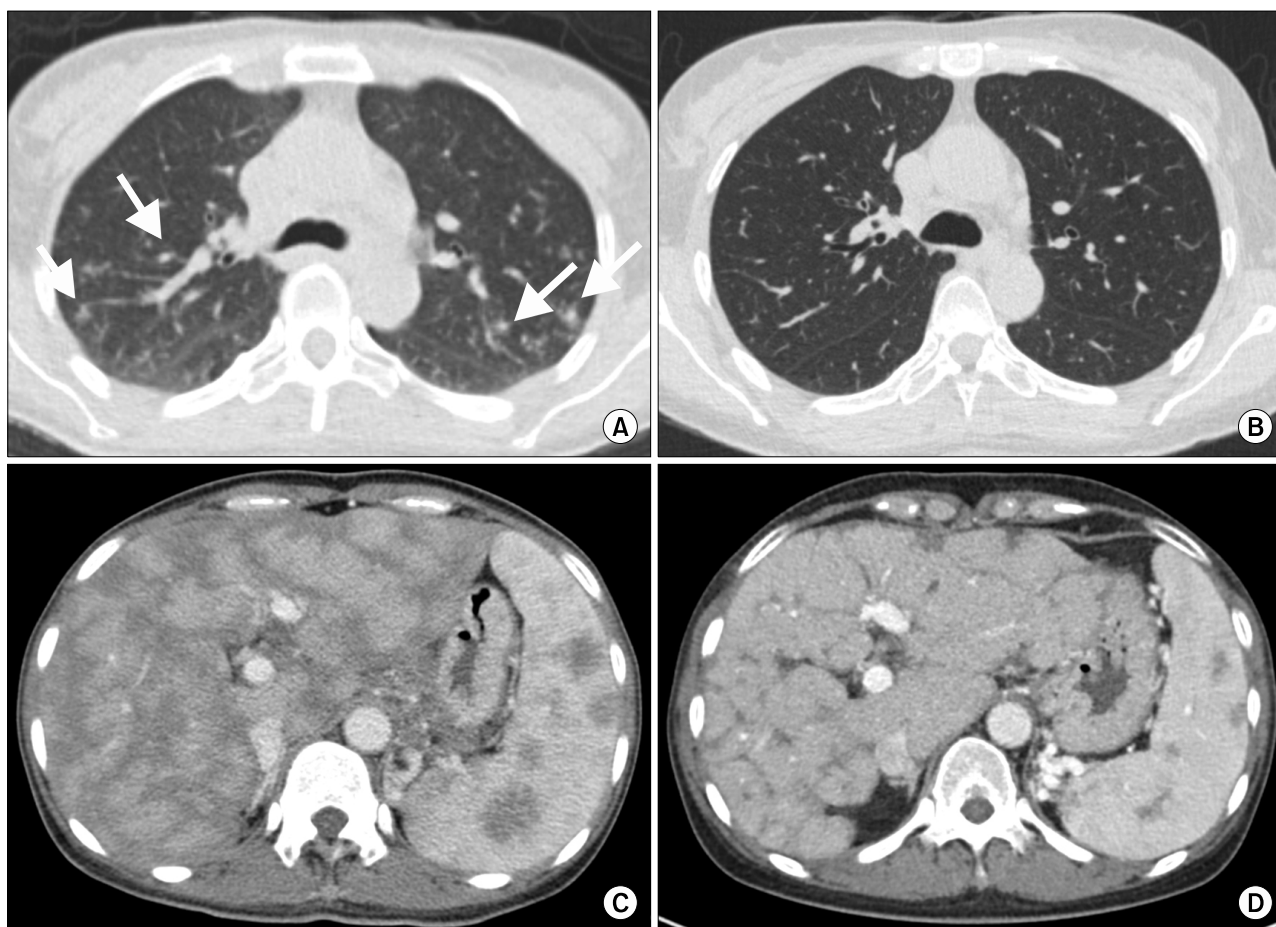


**Figure 3.** Positron emission tomography scan with multiple uptakes in the liver, spleen, lymph nodes, and bones.

liver and spleen, multiple lymph nodes uptake and hyper-metabolic foci in bones including L3 vertebra, left iliac bone, sacrum and right proximal femur (Figure 3). Since thrombocytopenia abruptly occurred and progressed in addition to increased bone uptake on PET scan, bone marrow biopsy was done and there were no abnormal findings. Thrombocytopenia might have been due to the liver cirrhosis. However, other manifestations of liver cirrhosis such as hyperbilirubinemia, hypoalbuminemia and prothrombin time prolongation were not remarkable. Therefore we suspected that hepatic sarcoidosis with marked splenomegaly might have induced the thrombocytopenia [9].

Under the diagnosis of sarcoidosis, auto-immune markers and angiotensin-converting enzyme (ACE) level were checked. ACE level was elevated to 180 U/L (20 to 70 U/L) and auto-immune markers including antinuclear antibody and rheumatoid factor were negative.

She was diagnosed with sarcoidosis involving liver, lung



**Figure 4.** Chest computed tomography (CT) scans (A, B) and abdominal CT scans (C, D). CT scans at the time of diagnosis (A, C) showing multiple perilymphatic nodules in both lungs (arrows) and heterogeneous enhancement in liver and spleen with hepatosplenomegaly. CT scans (B, D) taken after steroid treatment, revealing near total resolution of perilymphatic nodules and decreased size of liver and spleen.

and multiple lymph nodes, but no other organ involvement was found in such as eyes, skin or joints. She began to receive prednisolone at a dose of 30 mg/d. Follow-up CT scan was performed and it revealed improvement of sarcoidosis in liver as well as lymph nodes (Figure 4). The laboratory results were all within normal reference range. Prednisolone was tapered to a dose of 16 mg/d on the last visit.

## DISCUSSION

So far, there have been many reports that described the association between sarcoidosis and HCV. The first case was reported by Blum et al. [10] in 1993. Also, IFN- $\alpha$  for the treatment of HCV was believed to provoke the development of sarcoidosis by inducing various autoimmune conditions and disorders of immune regulation [11]. In

1999, Belgodere et al. [12] first reported a case of a HCV patient with sarcoidosis who had never been treated with IFN- $\alpha$ . It showed that IFN- $\alpha$  therapy may activate the development of sarcoidosis, but HCV infection itself also can induce sarcoidosis.

On the other hand, the report regarding the association between sarcoidosis and HBV is very rare; to our knowledge, there was only one case report by Husa et al. [13] in 2002. In that report, sarcoidosis was developed after the initiation of IFN- $\alpha$  for HBV treatment. But so far, there was no case report on sarcoidosis in patients with chronic HBV infection who were not treated by IFN- $\alpha$ .

In this case, the patient had been diagnosed with chronic HBV infection, but had never been treated by drugs including IFN- $\alpha$ . Thus we guessed the possible link between hepatic sarcoidosis and HBV infection.

So far, there are a number of reports about the relation-

ship between sarcoidosis and HCV infection. However, the studies regarding HBV infection is scarce. We speculate that the different cytokine profiles in HBV and HCV infection might be the reason for this different incidence of sarcoidosis. For example, higher amounts of IFN- $\gamma$  are secreted in HCV infection than in HBV infection [14]. And in the pathogenesis of sarcoidosis, high expression of T helper 1 cytokines such as IFN- $\gamma$  and interleukin-2 is noted [15].

However, the exact mechanism still remains unclear due to the lack of reports. But it can be reasonably assumed that the alterations in the pool of cytokines and immune cells caused by HBV infection may have a vicious influence on the immune regulation and in turn it can be a trigger for granuloma formation.

## SUMMARY

This report describes the first case of hepatic sarcoidosis accompanied by portal hypertension and liver cirrhosis in a patient with INF- $\alpha$ -naïve chronic HBV infection.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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