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CASE REPORT

Hepatic sarcoidosis complicating treatment-naive viral hepatitis

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Abstract

Hepatic sarcoidosis is usually asymptomatic but rarely leads to adverse liver-related outcome. Co-existence of viral hepatitis and hepatic sarcoidosis is a rare, but recognised phenomenon. Obtaining a balance between immune suppression and anti-viral therapy may be problematic. Immunosuppression in the presence of viral hepatitis can lead to rapid deterioration of liver disease. Similarly, anti-viral therapy may exacerbate granulomatous hepatitis. Here we present two cases of viral hepatitis co-existing with sarcoidosis that illustrate successful management strategies. In one, hepatitis B replication was suppressed with oral anti-viral therapy before commencing prednisolone. In the second, remission of hepatic sarcoidosis was achieved with prednisolone, before treating hepatitis C and obtaining a sustained virological response with pegylated interferon and ribavirin therapy.

Key words: Hepatic sarcoidosis; Chronic hepatitis C infection; Chronic hepatitis B infection; Immune suppression; Anti-viral therapy

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INTRODUCTION

Sarcoidosis is a progressive multi-organ disease of unknown aetiology, characterised histologically by the presence of non-caseating granulomas[1]. Clinical manifestations range from asymptomatic disease to multi organ failure. Hepatic involvement usually presents with abnormal liver biochemistry. Cirrhosis and liver failure are rare complications[2,3].

Co-existence of sarcoidosis and chronic viral hepatitis could accelerate liver fibrosis progression. Corticosteroids remain the mainstay of treatment for sarcoidosis. Treatment of hepatic sarcoidosis leads to symptomatic and biochemical improvement but may not necessarily impact disease progression[4]. On the other hand, immunosuppression with steroids could accelerate liver disease progression in patients with viral hepatitis. This phenomenon has been well documented with immune suppression during chemotherapy in patients with chronic hepatitis B virus (HBV)[5,6] and after liver transplantation.

Here, we report two cases of hepatic sarcoidosis complicating treatment-naive chronic HBV and hepatitis C

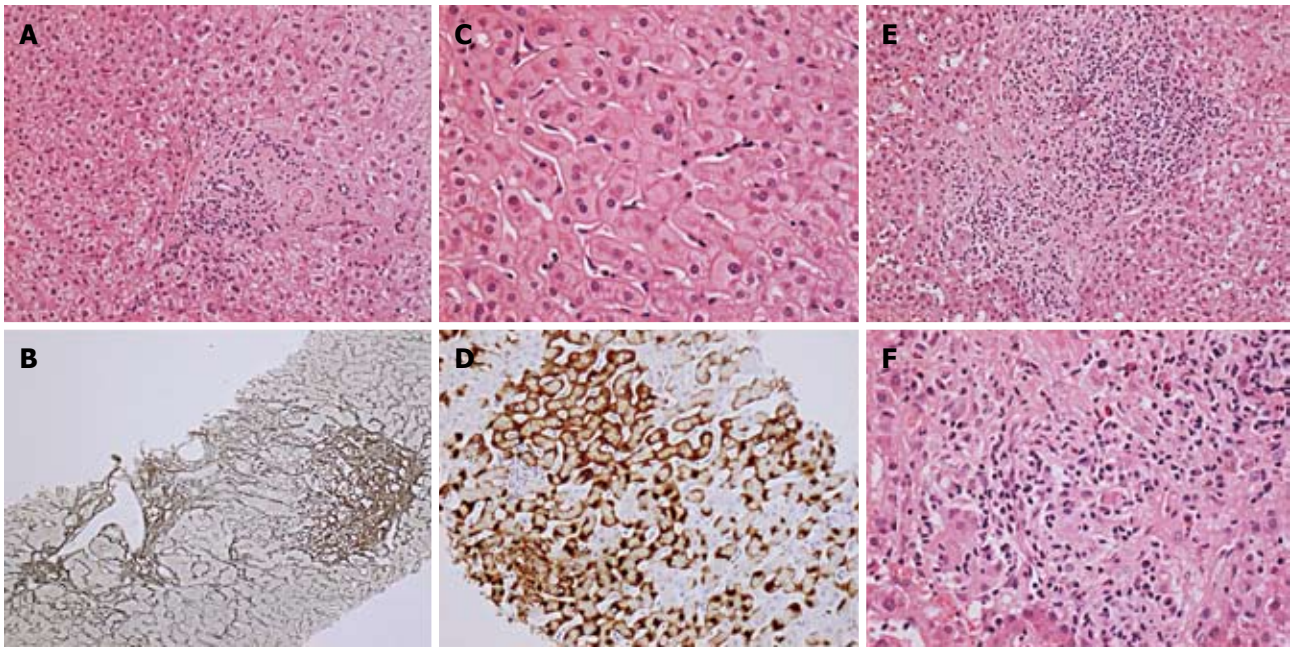

Figure 1 The histological features of hepatic sarcoidosis complicating chronic hepatitis B virus infection. A: Portal tract showing minimal portal inflammation attributable to hepatitis B virus [haematoxylin eosin (HE) staining ×20]; B: Portal fibrosis (reticulin ×40); C: Ground glass hepatocytes (HE ×40); D: Hepatitis B surface antigen immunostain showing accumulation in cytoplasm (×20); E: Granulomatous portal tract inflammation with duct irregularity (HE ×20); F: High power portal granulomatous inflammation (HE ×40).

virus (HCV).

CASE REPORT

Case 1

A 36 years old Ghanaian lady presented with abnormal liver biochemistry. Alanine transaminase (ALT) and alkaline phosphatase (ALP) were raised at 72 IU/L and 138 IU/L respectively (normal range ALT 0-54 IU/L; ALP 25-120 IU/L). Other than her country of origin, there were no risk factors for liver disease. A screen for chronic liver diseases demonstrated markers of chronic HBV carriage [hepatitis B surface (HBs) antigen positive, hepatitis B e (HBe) antigen negative, HBe antibody positive, HBV DNA 11 686 IU/L], but was otherwise unremarkable. Liver biopsy showed features of chronic HBV infection with moderate activity and moderate fibrosis. There were numerous ground glass hepatocytes and positive immunohistochemistry for HBs antigen (Figure 1A-D). Immunostaining for hepatitis B core antigen was negative implying low replicative activity. Additionally, there was non-caseating granulomatous portal inflammatory infiltrate (Figure 1E and F) noted. There was widespread mediastinal lymphadenopathy on computed tomography scanning, and the angiotensin converting enzyme (ACE) level was elevated (110 IU/L; normal range 12-68 IU/L). Other causes of granulomatous hepatitis were excluded.

Given moderate fibrosis on liver biopsy, lamivudine and adefovir were commenced. After 2 mo treatment, HBV replication was suppressed (HBV DNA < 100 IU/L), but abnormal liver biochemistry persisted. Prednisolone was therefore added to her regimen. Liver biochemistry and serum ACE level normalized (Figure 2), and HBV DNA remained undetectable though 24 mo follow-up. Current therapy consists of lamivudine, adefovir and prednisolone 10 mg.

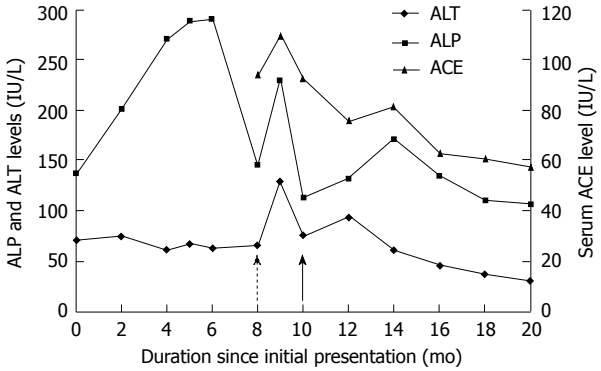

Figure 2 The changes in alanine transaminase, alkaline phosphatase and angiotensin converting enzyme levels in patient 1. The dotted arrow and the solid arrow mark the commencement of antiviral treatment and steroid treatment respectively. ALT: Alanine transaminase; ALP: Alkaline phosphatase; ACE: Angiotensin converting enzyme.

Case 2

A 37 years old man from Pakistan presented with a significantly elevated ALT level (532 IU/L, normal range 0-54 IU/L). Other than his country of origin, there were no risk factors for liver disease. A screen for chronic liver diseases demonstrated markers of chronic HCV carriage (HCV antibody positive, HCV RNA 4 450 000 IU/mL; genotype 3a), but was otherwise unremarkable. Liver bi-

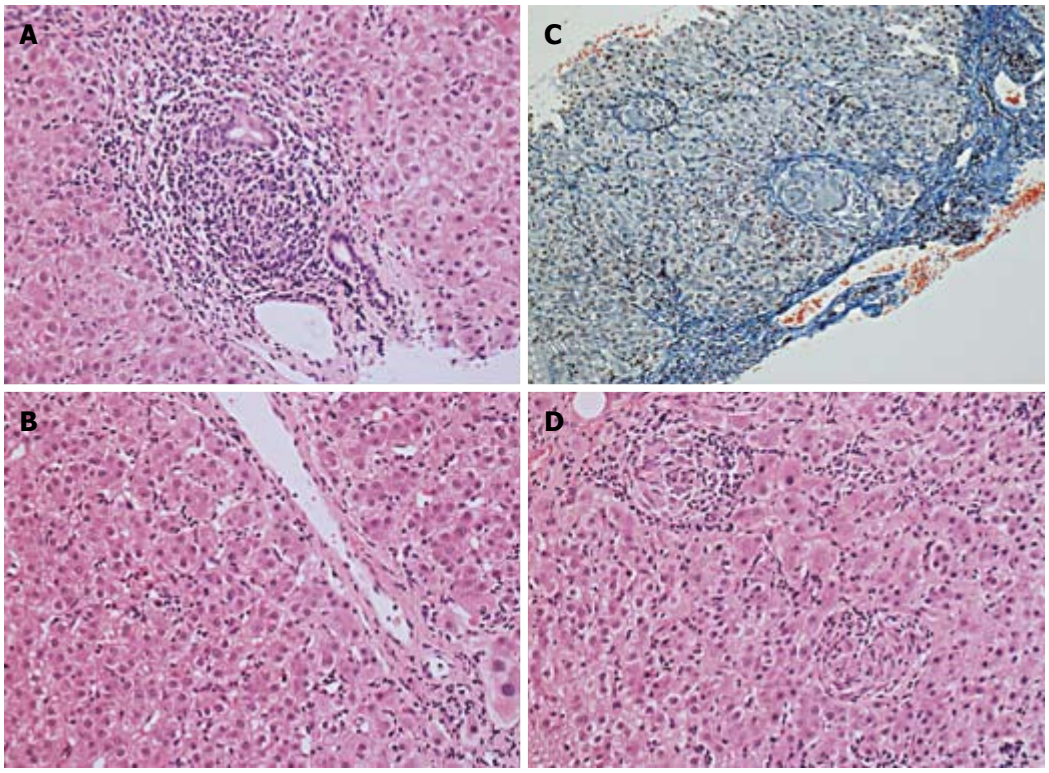

Figure 3 Histological features of hepatic sarcoidosis complicating chronic hepatitis C virus infection. A: Portal inflammation including lymphoid follicle and interface activity [haematoxylin eosin (HE) staining × 20]; B: Parenchymal inflammation and necroinflammation with acidophil bodies (HE ×20); C: Architectural stain showing parenchymal granulomatous inflammation and fibrosis (Chromotrope-Aniline Blue ×10); D: Parenchymal granulomatous hepatitis (HE ×20).

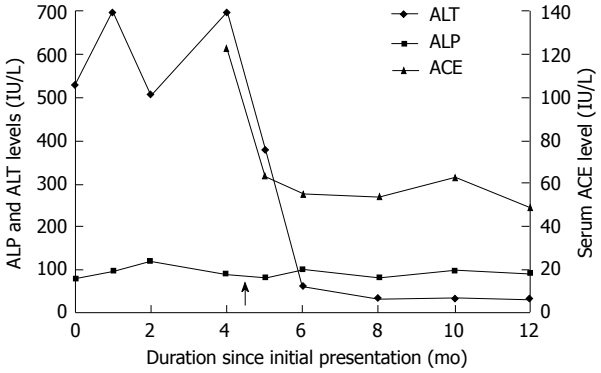

Figure 4 The changes in alanine transaminase, alkaline phosphatase and angiotensin converting enzyme levels in patient 2. The arrow marks the commencement of steroid treatment. ALT: Alanine transaminase; ALP: Alkaline phosphatase; ACE: Angiotensin converting enzyme.

opsy showed a moderately active portal and lobular hepatitis attributable to chronic HCV infection (Figure 3A and B) with moderate fibrosis. In addition, there were numerous small, well formed epithelioid granulomata seen throughout the lobule representing a granulomatous hepatitic component (Figure 3C and D). There was widespread mediastinal lymphadenopathy on computed tomography scanning, and the ACE level was elevated (124 IU/L). Other causes of granulomatous hepatitis were excluded with appropriate investigations. Steroid therapy was commenced and there was rapid normalisation of ALT and ACE levels (Figure 4). Following this, he received antiviral treatment with peginterferon alpha-2a 180 micrograms and ribavirin 400 mg twice daily for 24 wk. A sustained virologic response was achieved. He was maintained on prednisolone 10 mg throughout his antiviral treatment and thereafter.

DISCUSSION

Hepatic granulomas may be observed on liver biopsies from patients with hepatitis C[7,8], hepatitis B[9] and hepatitis A[10,11]. The incidence of hepatic granulomas in chronic HCV has been estimated at between 1%[7] and 10%[8]; in chronic HBV it is about 1.5%[9]. However, sarcoidosis complicating chronic viral hepatitis is rare. A number of case reports describe hepatic sarcoidosis in patients receiving antiviral treatment for HCV[12-18]. Here we report two cases of sarcoidosis complicating treatment-naïve chronic HBV and HCV. Sarcoidosis in untreated HBV is previously unreported.

Causes of hepatic granulomas include sarcoidosis, primary biliary cirrhosis, autoimmune hepatitis, drug-induced hepatotoxicity, lymphoma, viral hepatitis, tuberculosis, cytomegalovirus, leishmaniasis, toxoplasmosis, Q fever, fungal infections and antiviral treatment such as interferon, ribavirin and amantidine[8,19-21]. As for our patients, the diagnosis of hepatic sarcoidosis relied on demonstration of non-caseating granulomas and exclusion of other causes[22]. Whilst HCV and HBV may cause granulomatous hepatitis[7-9], the elevated serum ACE levels, extensive lymphadenopathy and steroid responsiveness supports a diagnosis of sarcoidosis in both cases.

The majority of patients with hepatic sarcoidosis are asymptomatic and the general consensus is to reserve treatment for patients with abnormal liver biochemistry[23]. Our cases fulfilled this criterion and deomonstrated normalization of liver tests with steriod therapy. For case 1,

abnormal liver biochemistry persisted despite HBV supression and then resolved with steroid therapy. For case 2, it was felt that the ALT level was much higher than what is usually seen in chronic HCV with moderate disease alone. This high ALT level and features of marked granulomatous hepatitis on liver biopsy led to initial therapy to be directed at sarcoidosis as this was considered to constitute the primary cause of liver injury. The ACE level dropped and liver biochemistry normalized with steroid therapy, even before the commencement of anti-viral therapy. Previous reports have documented a relapse of sarcoidosis with interferon treatment of HCV[15-18]. However, our patient (case 2) underwent successful therapy with pegylated interferon and ribavirin without such relapse.

In conclusion, hepatic sarcoidosis in combination with chronic viral hepatitis is uncommon. Our cases demonstrate that immune suppressive therapy in combination with appropriate timed antiviral therapy can be successful.

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