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CASE REPORT

Granulomatous Hepatitis in a Patient with Chronic Hepatitis C Treated with Interferon-α

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KEY WORDS: granulomatous hepatitis; chronic hepatitis C; interferon-α

Hepatitis C virus (HCV) is the main etiologic agent responsible for both transfusion-related and sporadic non-A, non-B hepatitis (1). Interferon-α (IFN-α) is known to reduce viral replication and normalize transaminase levels in about 40% of patients with chronic hepatitis C (2). Hence, it has become the standard therapy approved for chronic HCV infection.

IFN may cause many different adverse effects including flulike illness, bone marrow suppression, psychiatric disorders, and exacerbation of various autoimmune disorders, with autoimmune hepatitis and thyroiditis being the most common (3, 4). Granuloma formation has not been reported as an adverse effect of IFN-α treatment except in one case in which a patient developed pulmonary sarcoidosis during therapy with IFN-β for advanced renal cell carcinoma metastatic to mediastinal lymph nodes (5). Herein, we report the first case of granulomatous hepatitis induced by IFN-α in a patient with chronic hepatitis C.

CASE REPORT

A 48-year-old black female was referred to the UPMC in May 1994 for treatment of chronic HCV infection. Her main symptoms were fatigue and occasional right upper quadrant abdominal pain. There was no history of jaundice, blood transfusions, intravenous drug abuse, alcohol abuse, family history of liver disease, or exposure to hepatotoxic chemicals. Physical examination did not reveal any stigmata of chronic liver disease.

Laboratory tests were as follows: alanine aminotransferase (ALT) 96 IU/liter (<40), aspartate aminotransferase (AST) 106 IU/liter (<40), γ-glutamyltransferase (GGTP) 339 IU/liter (<65), alkaline phosphatase 98 IU/liter (40–125), total bilirubin 0.6 mg/dl (0.3–1.5), albumin 3.6 g/dl (3.5–5.5), polyclonal gammaglobulins 2.79 g/dl (0.7–1.6), prothrombin time 11.9 sec (11.2–14.4), platelet count 196,000/mm^3, anti-HCV antibody test by second generation EIA was positive; hepatitis B core antibody was positive but the rest of the hepatitis B serologies were negative. Antinuclear, anti-smooth muscle, anti-mitochondrial, anti-liver/kidney microsomal, and anti-thyroglobulin antibodies were all negative.

Abdominal CT scan showed a normal liver with no focal mass lesions. Pretreatment percutaneous liver biopsy performed in July 1994 showed prominent portal inflammation with lymphoid aggregates, piecemeal necrosis, and bridging fibrosis but no cirrhosis (Figure 1). These findings were consistent with chronic hepatitis C. Hepatitis activity index (HAI) was 13/22 (6). Hepatic HCV-RNA determined by reverse transcriptase polymerase chain reaction was positive.

Following the confirmation of chronic hepatitis C infection, the patient started on subcutaneous interferon-α_{2b}, 5 million units three times a week. Subsequent to IFN-α treatment transaminase levels decreased but never became normal. The patient continued to complain of increasing fatigue and abdominal pain. After completing six months of interferon treatment (February 1995), she underwent a second liver biopsy, which showed a moderate degree of portal and lobular inflammation with bridging fibrosis. There was a slight reduction in the degree of piecemeal necrosis as compared to the previous biopsy. Also seen were numerous portal based noncaseating granulomata (Figure 2). Hepatic HCV-RNA was still positive; HAI was 12/22. Special stains for fungi and acid-fast bacteria were negative. Hilar lymphadenopathy or interstitial pulmonary changes could not be demonstrated on repeated chest x-rays. Serum angiotensin-converting enzyme and calcium levels were

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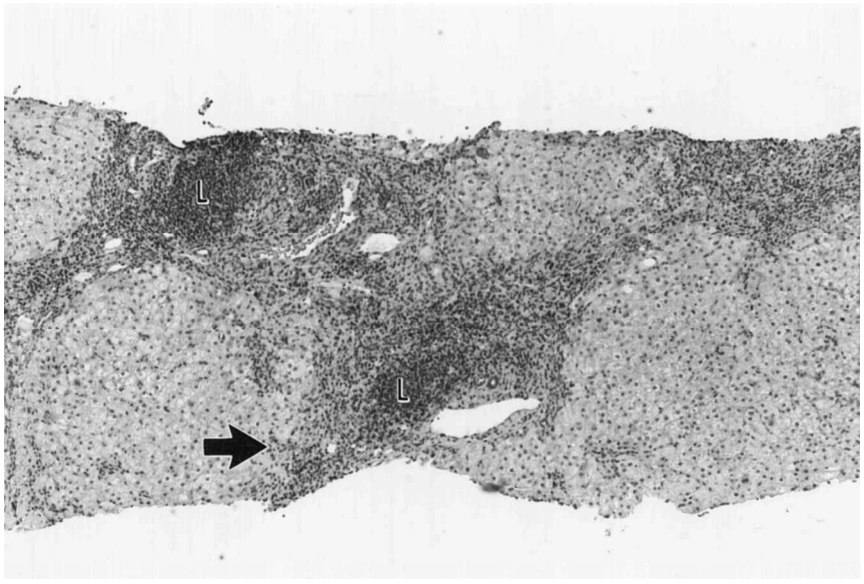

Fig 1. Pretreatment liver biopsy. Portal areas contain moderate chronic inflammation including lymphoid nodules (L). Limiting plates show patchy piecemeal necrosis (arrow). Hematoxylin–eosin, ×40.

normal; gallium scan was negative. PPD skin test was negative.

Because of failure to respond to IFN-α combined with the development of granulomatous inflammation as an unexpected side effect, we decided to discontinue further IFN-α therapy. Six months after cessation of IFN treatment, she underwent another liver biopsy (August 1995) that showed persistent portal and lobular inflammation with areas of bridging fibrosis. No granulomas could be demonstrated (Figure 3).

DISCUSSION

The common etiologies for granulomatous hepatitis include infections of different types, sarcoidosis,

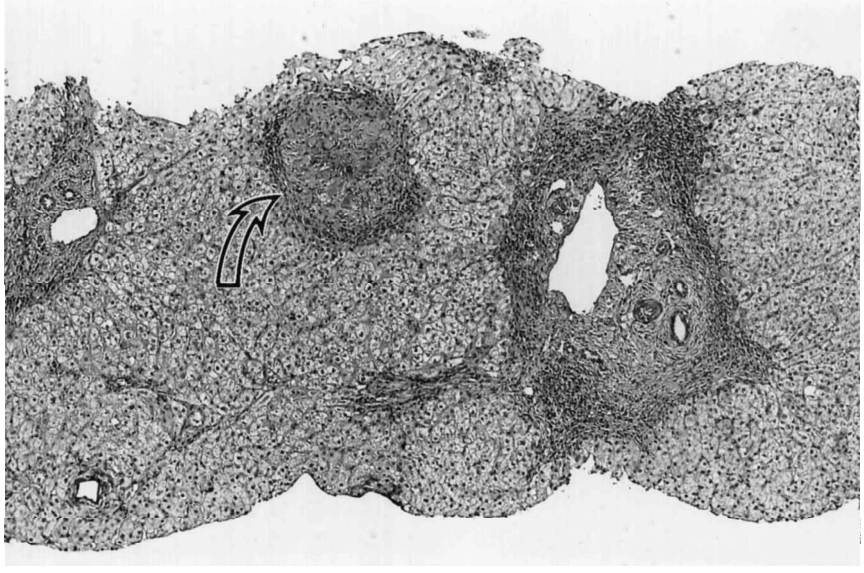

Fig 2. Liver biopsy at cessation of interferon treatment. Large, well-formed, noncaseating granulomas have developed (arrow). Note marked reduction in portal chronic inflammation and piecemeal necrosis. Hematoxylin–eosin, ×40.

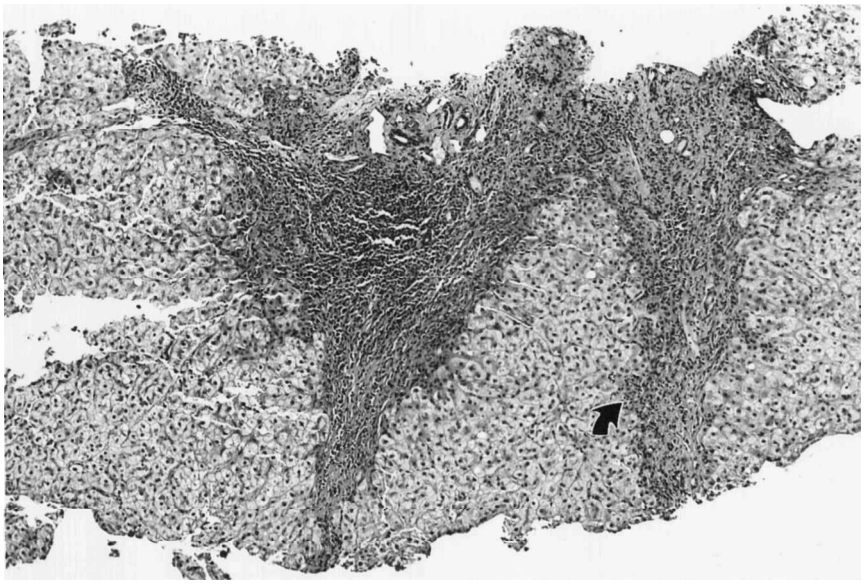

Fig 3. Liver biopsy six months after cessation of interferon. Granulomatous inflammation is no longer evident. Liver shows bridging fibrosis with a return of chronic inflammation and piecemeal necrosis (arrow).

drugs, Crohn's disease, primary biliary cirrhosis (PBC), and neoplasms (7). In a retrospective study of 88 patients with granulomatous hepatitis, the two most common causes were sarcoidosis and so-called "idiopathic" (8). In another study of 95 cases of granulomatus hepatitis, the two most common causes were sarcoidosis (31%) and drug-related (29%). Idiopathic granulomtous hepatitis was responsible for 12% of the cases (9).

Hepatitis C virus has also been associated with granuloma formation (10). Five of 52 patients (10%) who underwent orthotopic liver transplantation for HCV-related cirrhosis, had epithelioid granulomas with multinucleated giant cells in their explanted livers. No other causes for granuloma formation could be found in those cases. Of note, the granulomas were located within the regenerating nodules and never in the fibrous bands or portal tracts, as is usually the case in sarcoidosis. It should be noted that other investigators who examined 104 liver biopsy specimens of patients with chronic hepatitis C have not found granulomas (11, 12). In these series, however, only about half had cirrhosis as opposed to the previous series (10) in which all patients studied had cirrhosis. It is possible that HCV-induced granulomas are formed only in a cirrhotic stage.

It is unlikely that granulomata were missed in the first and last biopsies, as large cores of tissue were processed in both instances (15 × 1 mm). In addition, investigations performed before and after IFN treatment showed no evidence for sarcoidosis or any other possible cause of granulomata formation such as drugs, tuberculosis, fungal infection, or PBC. Although hepatitis C virus itself may induce granuloma formation (5), it is unlikely that it was the mechanism in our case as the granulomas disappeared despite an on going HCV infection.

Granulomas are small 0.5 to 2-mm collections of modified macrophages called epithelioid cells usually surrounded by lymphocytes (13). The source of the epithelioid cells is blood macrophages. These cells are capable of extracellular secretion of cytokines rather than classic phagocytosis. Another feature of the granuloma is the presence of Langhan's or foreign body-type giant cells that are the result of epithelioid cell fusion. These cells may contain up to 50 nuclei. Other cells seen in a granuloma are fibroblasts, plasma cells, and neutrophils (13).

The granulomatous inflammatory response is determined by two main factors: (1) the presence of undigestible organisms or particles, and (2) an enhanced cell-mediated immune response to an infectious agent. Indeed, IFN-γ and IL-4 were found to enhance *in vitro* transformation of macrophages to epithelioid and giant cells (14–16). It is unclear whether IFN-α can stimulate granuloma formation as IFN-γ does. Nonetheless, we hypothesize that by enhancing expression of class I MHC antigens, IFN-α enhances the immune response against infected cells. This in turn will stimulate the production and secre-

tion of cytokines which may lead to granuloma formation. It is unclear, however, why granulomas have not been documented more often in patients with chronic hepatitis C treated with IFN-α.

In summary, IFN may induce granuloma formation in patients with chronic hepatitis C. This condition is quite rare in light of the number of liver biopsies that have been performed in patients treated with IFN-α. The effect of these granulomas on the outcome or future response to treatment in these rare cases has yet to be determined.

SUMMARY

Common adverse effects of IFN-α include flulike symptoms, headache, irritability, and bone marrow suppression. Hepatic side effects are unusual except in patients with pretreatment autoimmune hepatitis. Granuloma formation in the liver as a result of IFN-α therapy has never been reported. We described a 48-year-old female with chronic hepatitis C infection who developed granulomatous hepatitis following treatment with IFN-α. The granulomatous inflammation resolved after discontinuation of IFN-α treatment. Possible mechanisms for this unusual occurrence are discussed.

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