Development of Rheumatoid Arthritis after Chronic Hepatitis Caused by Hepatitis C Virus Infection

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We describe a patient with rheumatoid arthritis (RA) who had preceding evidence of post-transfusion, non-A, non-B hepatitis. The patient showed positive serological tests for anti-hepatitis C virus (HCV) antibody. The manifestations of RA, including progressive polyarthritis and positive serum rheumatoid factors, emerged after the amelioration of hepatitis and persisted for more than 3 years, indicating that the polyarthritis in this patient was not the prodrome of the hepatitis. This patient had HLA-DR4 and HLA-Bw54 which are found to be strongly associated with RA in Japan. It is therefore suggested that HCV may trigger the development of RA especially in genetically susceptible individuals.
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Key words: rheumatoid factor, HLA-Bw54, HLA-DR4

Introduction

The development of rheumatoid arthritis (RA) has been considered to involve both genetic and environmental factors (1). Thus, the association of RA with HLA-DR4 has been well appreciated irrespective of the race (2–4). On the other hand, the association of arthritis with hepatitis has been well documented (5–12). The polyarthritis in most patients with viral hepatitis has been found to emerge during the prodrome of hepatitis, and to subside after the development of typical manifestations of hepatitis, resulting in no joint deformity (6). However, there has been a single case report in which the patient developed progressive RA subsequent to acute, hepatitis B surface antigen-positive, viral hepatitis (13).

Recently, a cDNA clone which was shown to encode an antigen associated with the non-A, non-B hepatitis has been isolated (14, 15). This non-A, non-B hepatitis virus, designated hepatitis C virus (HCV), appears to account for 70–80% of the non-A, non-B hepatitis (16). In the present report, we describe a patient who developed progressive RA after post-transfusion HCV infection. The possible role of HCV in the triggering of the development of RA in genetically susceptible individuals is discussed.

Case Report

A 55-year-old woman visited our clinic with the complaint of general malaise on April 8, 1986. She was found to have mild liver dysfunction in 1983. Laboratory examination on her visit revealed a slight elevation of serum transaminases (GOT 31 KU, GPT 25 KU). She had received a blood transfusion in 1957. She denied habitual intake of alcohol or drugs. Serological tests for hepatitis A virus (HAV) and hepatitis B virus (HBV) infection were all negative. The diagnosis of chronic hepatitis of a non-A, non-B type was made. At this time, she did not show any joint manifestations and the RA test was negative. In July 1987, she visited our clinic again with the complaint of painful polyfocal joint swelling and morning stiffness of her hands lasting more than 3 months (Fig. 1). Physical examination revealed painful symmetrical swelling of the proximal interphalangeal (PIP), metacarpophalangeal (MCP) and knee joints. Laboratory data showed normal liver function test. The result of C-reactive protein was 1 + positive, and erythrocyte sedimentation rate was 51 mm/h. She was diagnosed as RA, and treatment with oral prednisolone (2.5 mg/day) and indomethacin (50 mg/day) was started. Her liver function test has remained normal since July 1987. However, her RA has not been satisfactorily controlled by the additional treatment with disease modifying

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Fig. 1. Clinical course of the patient showing the development of rheumatoid arthritis (RA) after long lasting chronic hepatitis due to hepatitis C virus (HCV) infection.

anti-rheumatic drugs, as evidenced by the findings on roentgenograms of the joints showing remarkable erosive changes (Fig. 2). She had been diagnosed as post-transfusion non-A, non-B hepatitis because of the negative results for HBs Ag and anti-HBs antibody. Serological examination using an assay kit for anti-HCV antibody (Chiron Co., Emeryville CA) revealed the positive anti-HCV antibody in the sera, indicating that her hepatitis was caused by HCV infection. The test for anti-HTLV-I antibody was negative. Although RA test turned positive when she developed active synovitis, she had shown negative serum rheumatoid factor during the phase of active hepatitis without joint manifestations. The results

of HLA analysis disclosed that the present patient possessed the combination of HLA-DR4 and HLA-Bw54 which has been reported to be associated with RA in the Japanese population (17), indicating that she was genetically susceptible to RA.

Discussion

We describe a patient who developed RA after post-transfusion HCV infection. The association of arthritis with viral hepatitis has been well documented (5–12). However, polyarthritis in patients with acute viral hepatitis usually emerges during the prodrome of hepatitis and subsides with the development of the typical manifestation of hepatitis, leaving no joint deformity (6). In chronic active viral hepatitis, polyarthralgia may present with the early systemic manifestations of the disease (6). The polyarthritis noted in the present patient differs from such arthritides in patients with viral hepatitis in a number of aspects. First, the polyarthritis in the present patient developed after the hepatitis had subsided. Secondly, the polyarthritis was long lasting and progressive to result in joint destruction. Finally, although the serum rheumatoid factor was positive along with the presence of active synovitis, our patient showed negative serum rheumatoid factor during the phase of active hepatitis without joint manifestations. Together with these findings, this patient fulfilled the 1987 revised American Rheumatism Association criteria for rheumatoid arthritis (18), indicating that the joint manifestations in our patients are due to the development of RA. Recently, human T cell leukemia virus type 1 (HTLV-I) has been found to cause chronic progressive synovitis resembling RA (19). However, the test for anti-HTLV-I antibody was negative in the present patient, obviating the possibility that the joint manifestations of this patient

Fig. 2. Roentgenogram of both hands taken on March 8, 1991, showing typical erosive changes.

might be caused by HTLV-I infections.

Although the relationship between hepatitis B and synovitis has been extensively studied, there has been only one case report describing the occurrence of RA as a sequel to HBs Ag hepatitis by Morris and Stevens (13). However, the possibility of double infection of HBV and HCV could not be excluded in their patient. On the other hand, there has been a report that 2 of 30 patients with RA without a history of hepatitis showed the positive serum anti-HCV antibody (20). It is therefore possible that HCV may contribute to the development of RA.

Although the etiology of RA is still unknown, there is a hypothesis that the disease may be triggered by one or more foreign antigens invading genetically susceptible individuals (1). The close association of HLA-DR4 with RA has been well appreciated irrespective of the race (2–4). As to the Japanese RA patients, however, combination of HLA-DR4 and HLA-Bw54 has been frequently observed (17). Interestingly, the present patient possessed a combination of HLA-DR4 and HLA-Bw54, indicating that she was genetically susceptible to RA. Therefore, it is suggested that HCV may trigger the development of RA in genetically susceptible individuals. Of course, we cannot exclude the possibility that HCV infection and the development of RA might have occurred in this patient by chance. Further studies are necessary to clarify the precise role of HCV in the development of RA.

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