Letter to the Editor
Diagnostic Immunology

Ann Lab Med 2015;35:660-662
http://dx.doi.org/10.3343/alm.2015.35.6.660
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Anti-Rods and Rings Autoantibodies in a Patient With Hepatitis C Virus Infection

Kyung Ho Choi, M.D.[1], Young Ae Lim, M.D.[1], Think-You Kim, M.D.[2], La-He Jearn, M.D.[2], Sae Yun Baik, M.D.[3], Sung Won Cho, M.D.[4], and Eunju Jeong, M.D.[4]

Departments of Laboratory Medicine[1] and Internal Medicine[4], Ajou University School of Medicine, Suwon; Department of Laboratory Medicine[2], Hanyang University School of Medicine, Seoul; Green Cross Laboratories[3], Yongin, Korea

Dear Editor

The fluorescent antinuclear antibody (FANA) test is widely used for the detection of systemic autoantibodies. Moreover, the fluorescent patterns seen with the FANA test have specific clinical significance [1, 2]. We recently observed an unfamiliar FANA pattern with several small cytoplasmic rod and ring immunofluorescence known as anti-rods and rings (RR) autoantibodies—the first instance in Korea—in a patient with hepatitis C virus (HCV) infection who received combined interferon (IFN) and ribavirin treatment [3-8].

A 69-yr-old man was admitted to Ajou university hospital in Korea in July 2014 for jaundice due to liver cirrhosis. On admission, his condition worsened owing to hepatic failure. He had been diagnosed as having HCV infection, hypertension, and type 2 diabetes in 2001. He refused medical care until 2009, when he received treatment with IFN and ribavirin for one year. The treatment was discontinued because of ineffectiveness. There was no other history of supportive treatment, including herbal medication.

On admission, the patient developed sudden jaundice with the following laboratory results: total bilirubin, 21 mg/dL; direct bilirubin, 15.0 mg/dL; ALT, 78 U/L; and AST, 265 U/L. As there were no previous FANA test data available, the physician requested a FANA test to rule out autoimmune hepatitis as the cause of hepatic failure [7]. The FANA test was performed by using the HEPANA test with HEp-2 cells (Medical & Biological Laboratories Co., Ltd., Nagoya, Japan) and was read with a Zeiss Axio Imager A1 (Carl Zeiss Inc., Germany).

A novel finding on the FANA test included several small cytoplasmic RR immunofluorescences (Fig. 1A). The result was reproducible with a titer of 1:640. Experts at another laboratory confirmed the pattern as anti-RR autoantibodies by using an autoimmune target (AIT) test (ImmunoThink Co., Seoul, Korea). Other reagents, such as HEp-2 ANA slides (INOVA Diagnostics, San Diego, CA, USA) also showed the RR pattern [3-8]. However, Kallestad HEp-2 cell line substrate (Bio-Rad Laboratories, Hercules, CA, USA) showed other cytoplasmic patterns, such as autoantibodies recognizing mitotic spindle apparatus-related antigens, instead of the RR pattern (Fig. 1B). This discrepancy may be due to differences in the conditions used for particular tissue cultures and the fixation of HEp-2 cells. Therefore, all commercial HEp-2 slides may not be reactive to anti-RR autoantibodies [6, 8].

The patient developed acute renal failure likely owing to hepatorenal syndrome at admission and died on day 17 post-admission despite supportive treatment.

Received: January 29, 2015
Revision received: May 8, 2015
Accepted: July 22, 2015

Corresponding author: Young Ae Lim
Department of Laboratory Medicine, Ajou University School of Medicine,
164 World Cup-ro, Yeongtong-gu, Suwon 16499, Korea
Tel: +82-31-219-5786, Fax: +82-31-219-5778
E-mail: limyoung@ajou.ac.kr

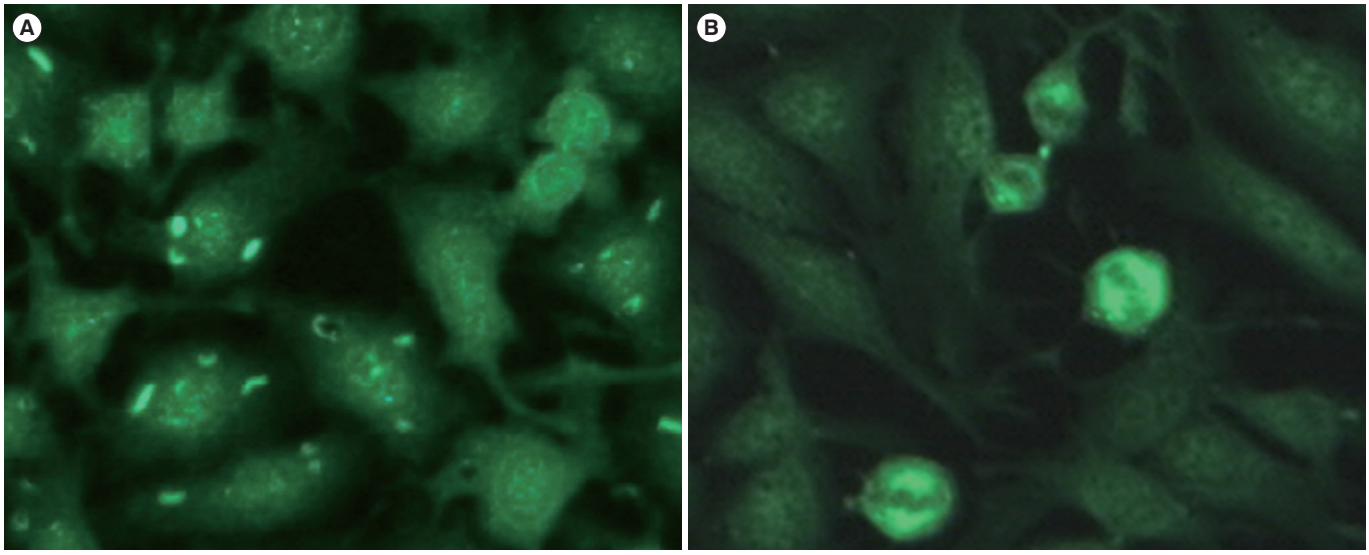

Fig. 1. (A) Cytoplasmic rods and rings of HEp-2 cells with FITC-conjugated goat anti-human immunoglobins (Medical & Biological Laboratories Co., Ltd., Nagoya, Japan) in sera from the patient with hepatitis C virus infection (×200). (B) Cytoplasmic pattern (autoantibodies recognizing mitotic spindle apparatus-related antigens) observed with Kallestad HEp-2 cell line substrate (Bio-Rad Laboratories, Hercules, CA, USA) in sera from the patient with hepatitis C virus infection (×200).

There have been several reports about the incidence of the anti-RR pattern with hepatitis C and other illnesses. It is present in approximately 30% of the patients with chronic hepatitis C treated with IFN-ribavirin [7], 14.1% with hepatitis C, and 3.4% with hepatitis B but has not been observed in patients without any form of viral hepatitis [8]. High anti-RR autoantibody titers occur in patients with no response or relapsers [3], although some studies found no association between anti-RR titer and treatment response [7, 8]. The patient's anti-RR titer was 1:640, which was high according to earlier reports [7, 8]. The patient did not respond to combination IFN and ribavirin therapy.

Anti-RR autoantibodies are reportedly detected more often in relapsers and non-responders than in sustained virological responders defined as having undetectable HCV RNA 24 weeks post-therapy [3, 4]. The viral load of the present patient, 196,254 copies/mL (72,687 IU/mL), exceeded the category limits of high viral load [7]. We detected no hepatitis B virus co-infection or other autoantibodies, including anti-mitochondrial antibody or anti-smooth muscle antibody. This patient's treatment with IFN and ribavirin was discontinued after a year owing to lack of effectiveness; hence, the patient appeared to be a non-responder [7].

We did not analyze the target antigens of anti-RR autoantibodies; several studies have reported that the target antigens of anti-RR autoantibodies are inosine monophosphate dehydrogenase 2 (IMPDH2), cytidine triphosphate synthase 1 (CTPS1), or both [3-5, 8]. These enzymes, which normally mask epitopes that might participate in RR formation, are inhibited by IFN and ribavirin treatment, which induces structural modifications that make the epitopes accessible to the immune system [5, 8]. Other potential target antigens, including Myc-associated zinc finger protein (MAZI), have also been reported and must be confirmed [6].

Anti-RR autoantibodies can easily be overlooked if clinical pathologists ignore specific FANA patterns; therefore, FANA patterns require cautious interpretation. The anti-RR autoantibody pattern should also be distinguished from other cytoplasmic patterns and reported as the cytoplasmic RR pattern. Clinical information on patient history and present illness is helpful in the interpretation of unusual or unfamiliar FANA patterns.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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http://dx.doi.org/10.3343/alm.2015.35.6.660