Case Report

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Pathology Section

Detection of Anti-Rod and Anti-Ring Autoantibodies in a Patient with Seronegative Rheumatoid Arthritis and Cirrhosis of Liver: A Case Report

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ABSTRACT

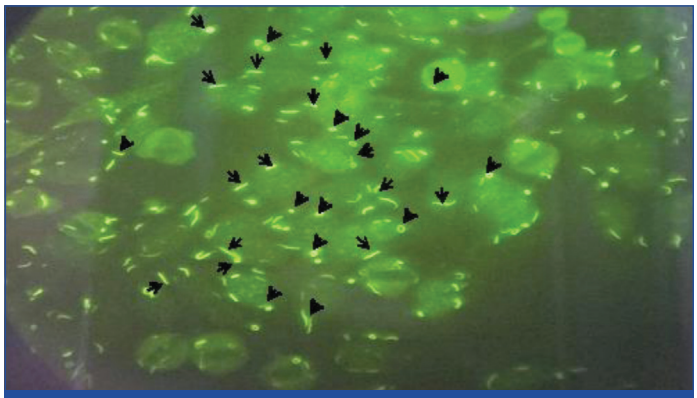
Present case (53-year-old female) relates to results of diagnostic autoantibodies reactive against various antigens. Autoantibodies reactive against 16 nuclear antigens (Mi-2, ku, nRNP/Sm, S5-A (nativ), RO-52, SS-B, Scl-70, PM-Scl100, jo-1, CENPB, PCNA, DsDNA, nucleosomes, histones, ribosomal P-protein) and antigen Anti-Mitochondrial M2 Antibody (AMA-M2) were tested by indirect enzyme-linked immunosolvent assay, using a membrane as the solid phase; no colour reaction developed, suggesting absence of antibodies against above antigens. However, autoantibodies against rod and ring-like structures Inosine Monophosphate Dehydrogenase (IMPD) were detected. Presence of high titer autoantibodies against Double stranded (Ds) Deoxyribonucleic Acid (DNA) and Sm nuclear antigens might be diagnostic of Systemic Lupus Erythematosus (SLE). However, low titer antibodies against other nuclear antigens might increase the risk to develop SLE in an asymptomatic patient. Immune complexes might develop and get deposited in synovium. Later, chronic synovitis might develop. In addition, the test for rheumatoid factor was negative with serum of the current patient. Patient was diagnosed as a case of seronegative rheumatoid arthritis. The patient also had cirrhosis of the liver. Rarely, anti-rod and anti-ring autoantibodies might develop in a patient with Hepatitis C Virus (HCV) infection. Further, these antibodies might also be detected in sera of patients with SLE or Hashimoto's thyroiditis or during treatment with interferon-α/ Ribavirin. However, the significance of these autoantibodies in pathogenesis of a autoimmune disease or HCV infection is unknown. High titer antibodies against double stranded (Ds) DNA and Sm antigens might be diagnostic of SLE.

Keywords: Antinuclear antibody, Inosine monophosphate dehydrogenase, Systemic lupus erythematosus

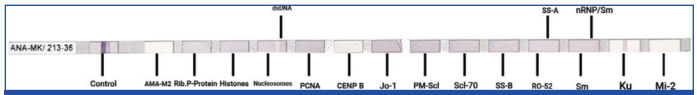
CASE REPORT

A 53-year-old female patient reported with chief complain of pain and swelling of small joints of both hands since 20 years. On examination, she had redness and swelling of proximal and distal interphalangeal joints of both hands. Test for serum rheumatoid factor was negative. Occasionally, she consumed alcohol and developed cirrhosis of liver three years ago. On abdominal examination, spleen was just palpable. She was diagnosed as a case of seronegative rheumatoid arthritis with compensated cirrhosis of liver and firbrocongestive spleen. Serum autoantibody was tested using Human Epidermal Growth Factor Receptor 2 (HER2) and monkey liver cells by indirect immunofluorescence test (kit was purchased from euroimmune dedizinische Labordiagnostika, Germany). Results of immunofluorescence test revealed detection of Rods and Rings (RR) like perinuclear cytoplasmic antigens [Table/Fig-1]. She was treated with Ibuprofen 200 mg thrice a day. However, at the time of writing this report, patient was not taking any medication.

Autoantibody profile (et Mi-2 et ku) was also used for detection of antibodies of IgG class against 16 different antigens, like Mi-2, Ku, nRNP/Sm, SS-A (native), Ro-52, SS-B, Scl-70, PM-Scl100, Jo-1, CENP B, PCNA, dsDNA/ nucleosomes, histones, ribosomal P-protein and AMA M2. Autoantibodies were tested in serum of the patient (test kit had parallel horizontal lines of highly purified antigens in immunoblot strips). Strip was incubated with diluted serum. Specific IgG antibodies (also IgM and IgA) would bind with the corresponding antigen. To detect the bound antibody, a second antibody (anti-human IgG alkaline phosphatase conjugate) was used. Later, a colour reaction was developed. Antibodies were not detected against above cellular antigens [Table/Fig-2].



[Table/Fig-1]: Shows rod (→) and ring (o) like cytoplasmic/perinuclear structures. Indirect immunofluorescence test was done on Hela cells. Patient's serum (1:100 dilution) was layered on Hela cells to allow reaction to occur. Later, cells were washed and anti-human Ig fluorescein conjugate was layered. Subsequently, the cells were examined for immunofluorescence.



[Table/Fig-2]: Shows results of different antigens by immunoblot test. First blot on left showed a positive control. Colour developed with positive control. No colour developed with patient's serum, suggesting absence of autoantibodies against 16 cellular antigens.

DISCUSSION

Contrary reports have been obtained regarding the role of Hepatitis C Virus (HCV) in pathogenesis of RR antigens [1]. For example, Shaikh Y et al., could not detect HCV in 38 RR patients and only one RR patient was also HCV positive [1]. In another study, Sener AG, reported three cases with RR antibody pattern out of 41921 sera

tested with anti-human IgG fluorescein conjugate [2]. Conversely, Keppeke GD et al., found one patient with Hepatitis B Virus (HBV) infection out of 57 RR cases (the remaining 56 cases were also HCV positive) [3]. Current case did not have HCV infection. Anti-rod and anti-ring (anti-RR) antibodies might develop during non responsiveness to interferon-α and ribavirin (IFN-α/RBN) treatment or following relapse [4]. Rarely, anti-RR antibodies were detected in a normal healthy individual with no previous history of INF-α/RBN treatment. Moreover, a few patients with Systemic Lupus Erythematosus (SLE) or Hashimoto's thyroiditis might also develop anti-RR antibodies. Sera of anti-RR positive patients also reacted with inosine 5'-monophosphate dehydrogenase 2 (IMPDH2) which appeared to be a major autoantigen of RR [5]. Additionally, autoantibodies against Cytidine Triphosphate Synthetase type-1 (CTPS1), a cytoplasmic antigen might also develop in a HCV patient being treated with IFN-α/RBN. These enzymes (IMPDH2 and CTPS1) appeared to mask the epitopes that might participate in RR formation. These enzymes are inhibited by INF-α and ribavirin [3]. In addition, Myc-Associated Zinc finger protein (MAZI) was also suspected to be a target antigen [6]. Anti-RR positivity suggested poor HCV treatment outcome [7].

Recently, Telaprevir (TPV) was included along with IFN-α/RBN as triple drug therapy for treatment of HCV infection. Present case was not treated with ribavirin (RBN). Moreover, TVP was also not given to current patient. Presence of anti-RR antibodies may also be explained by changes in immune-regulation caused by autoimmunity or Hepatitis C Virus (HCV) infection in a particular genetic background [8]. Another peculiarity of the current case was absence of anti-histone antibody in serum; anti-histone antibody might be detected in more than half of the cases of Rheumatoid Arthritis (RA). Anti-U1-nRNP antibody is rarely found in RA. In addition, RA might develop when a patient with HCV infection was treated with IFN-α and RBN [9]. Increased B-cell activity had been reported earlier in RA patients [10]. Moreover, the role of circulating immune complexes had been suspected in pathogenesis of ankylosing spondylitis [11]. These observations suggested that all the patients with arthritis might not be immunologically silent and immune alterations as well as other factors might contribute to formation of anti-RR antibodies. In another study, 66 samples with anti-RR antibody were detected and it was suggested that anti-RR in non hepatitis patients might be a manifestation of metabolic diseases [12]. Moreover, IMPDH might be the antigen detected by anti-RR antibody [13].

Detectin of anti-Ro antibody had been useful in the diagnosis of Systermic Lupus Erythematosus (SLE) and Sjögren's Syndrome (SS). Anti-Ro antibody might produce pathology in various organs and different symptoms might develop during the course of SS. Anti-Ro antibodies might produce necrosis as well as inhibit the activity of Ro52 antigen. Further, inverstigations in Ro autoantigen-autoantibody system might be required for the treatment of autoimmune diseases. Serum containing autoantibodies against Ro/SSA might recognise two different antigens (Ro52 and Ro60). Ro52 might reside in cytoplasm while Ro60 might reside in the nucleus. Further, Ro52 antigen might be coexpressed with Soluble Liver Antigen (SLA). Patients with dual autoantibodies had a high frequency of DRB1*03 when compared with DRB1*4 [14].

CONCLUSION(S)

The present case reports reported the anti-rod and anti-ring autoantibodies in serum of a patient with seronegative rheumatoid arthritis. Both serum rheumatoid factor and anti-HCV antibody tests were negative. There was no history of treatment with interferon-alpha and ribavirin. Presence of anti-rod and anti-ring (anti-RR) antibodies suggested the role of autoimmunity in pathogenesis of arthritis in current patient. Several factors appear to be involved in pathogenesis of anti-RR antibodies, for example, anti-HCV infection and treatment with interferon-alpha/ribavirin hepatitis B virus infection. Further, anti-RR antibodies might be detected in several autoimmune diseases, like systemic lupus erythematosus, Hashimoto's thyroiditis and/or rheumatoid arthritis.

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