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CLINICAL RELEVANCE OF ANTIKERATIN ANTIBODIES IN RHEUMATOID ARTHRITIS AND SYMMETRIC POLYARTHRITIS ASSOCIATED WITH HEPATITIS C INFECTION

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Summary: Chronic hepatitis C virus (HCV) has been linked to extrahepatic autoimmune phenomena. In addition, a variety of autoantibodies were found in patients with HCV. This study was performed to assess clinical relevance of antibodies in rheumatoid arthritis (RA) and in patients with symmeric polyarthritis associated with hepatitis C infection. Serum antikeratin antibodies were determined in 3 different groups of patients; all were rheumatoid factor (RF) seropositive Group 1:31 patients with HCV associated symmetric polyarthralgia or arthritis; Group 2: 28 patients with RA (modified ACR criteria for probable RA) Group 3:16 patients with autoimmune disorders other than RA. Seventeen healthy individuals matched for age and sex served as controls. In our study, 75 patients who were rheumatoid factor positive (measured by ELISA, the cutoff was established at 40 U/mL) were tested for antikeratin antibodies using an indirect immunofluorescence technique with 1:10 serum dilution. Antikeratin antibodies were detected in 18/28 (64%) patients with true RA and only 3/31 (9%) patients with HCV-related arthritis ($p<0.0001$). Antikeratin antibodies were observed in 3/16 (18%) patients of group 3 ($p<0.05$). Antikeratin antibodies were not found in the sera of healthy controls.

Key words: hepatitis C, rheumatoid arthritis, symmetric polyarthritis, antikeratin antibodies

Introduction

Hepatitis C is a widespread chronic liver disease. Autoimmunity may be observed in the chronic viral hepatitis, in particular hepatitis C. The hepatitis C virus (HCV) displays numerous interactions with the immune system (1). Hepatitis C virus (HCV) infection has been associated with a plethora of immune and autoimmune perturbations. The hepatitis C virus infects mononuclear cells and, like other viruses, can be responsible for immune disorders. Hepatitis C virus induces a number of diseases of presumed autoimmune background, like arthritis (2). HCV infection can be associated with the symmetric inflammatory polyarthritis. On the other hand, a number of autoantibodies are observed during the course of hepatitis C. The immune response to HCV may include the development of rheumatoid factors. There are reports of HCV infection preceding or coincident with polyarthritis and rheumatoid arthritis (RA) (3, 4).

Various viruses have been implicated in the cause and pathogenesis of rheumatoid arthritis (RA). Hepatitis C virus (HCV) infection has been recognised as the cause of some autoimmune diseases, and has been described as sometimes presenting with rheumatic manifestations indistinguishable from RA (5, 6).

The relationship of hepatotropic virus infection and the immune system leads to virus-associated autoimmunity (7). Virus-associated autoimmunity is still at the centre of the research activities aimed at establishing diagnostics. A positive association between rheumatoid arthritis (RA) and hepatitis C virus (HCV) infection has been reported in clinic studies (8).

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Our aim was to investigate whether antikeratin antibodies (AKA) could be useful in the differential diagnosis of patients with rheumatoid arthritis (RA), compared to patients with hepatitis C virus (HCV) associated polyarthritis who are seropositive for the rheumatoid factor (RF).

Materials and Methods

All patients were checked for the presence of HCV antibodies. Tests for rheumatoid factors was positive in all patients.

AKA were assayed in 3 different groups of patients; all were RF seropositive. Group 1:31 patients with HCV associated polyarthralgia or arthritis. Group 2: 28 patients with RA (modified ACR criteria for probable RA). Group 3:16 patients with autoimmune disorders other than RA. Seventeen healthy individuals served as controls (matched for age and sex).

IgG class antibodies to keratin have been detected in the serum stored at –20 °C. Antibodies to keratin were detected by the specific fluorescent staining of the stratum corneum of rat oesophagus. In addition to the oesophagus slide, an antikeratin-specific positive control is also available. The assay can be run using the standardised 90 min procedure and with common reagents including conjugate, mounting medium, systems negative control and PBS concentrate.

Results

A marker called AKA has been studied to differentiate true RA from HCV related arthritis. In our study, 75 patients who were rheumatoid factor positive (measured by ELISA, the cutoff was established at 40 U/mL) were tested for AKA using an indirect immunofluorescence technique with 1:10 serum dilution. Antikeratin antibodies were detected in 18/28 (64%) patients with true RA and only 3/31 (9%) patients with HCV-related arthritis ($p<0.0001$). Antikeratin antibodies were not found in the sera of the healthy controls. The results of the test for AKA are considered negative at the serum dilution $<1:10$.

Discussion

Hepatitis C virus (HCV) infection is given special attention because this virus has the propensity to induce various autoimmune phenomena (9). Identifying and understanding the pathophysiologic mechanisms by which viral arthritis causes acute and chronic arthropathies is crucial to understanding its immunopathogenesis (10). Alterations of the immune system can lead to acute forms of arthritis, which can be followed by chronic arthralgia or arthritis (i.e. overrepresentation of CD8+ T lymphocytes in the synovial fluid of individuals with rheumatoid arthritis) (11). The number of patients diagnosed with acute viral arthritis

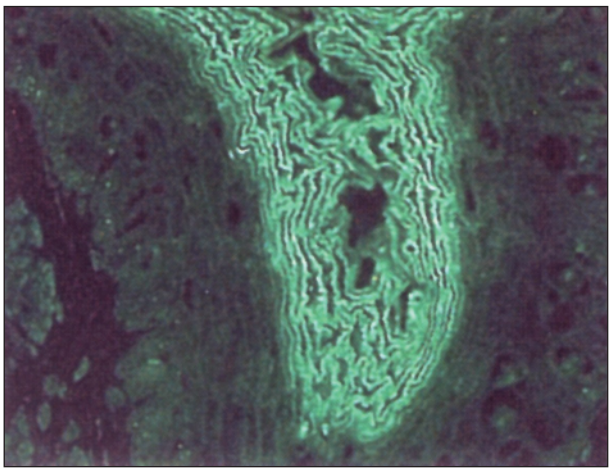

Figure 1 Antibodies to kreatin IgG are detected by the specific fluorescent staining of the stratum corneum of rat oesophagus

is relatively low because of its late presentation (12). Viruses are agents that cause infection, or are co-factors in the development of rheumatic diseases. Viral infection depends on host and viral factors. The immune complexes from an antibody response can be deposited at sites of viral infection or in the synovium (13).

This has prompted research aimed at identifying the link between hepatitis C and autoimmunity, and polyarthritis in particular (13). Myalgia (muscle pains), fatigue and arthralgias (joint pains) are common manifestations of HCV infection (14). HCV infection seems to be, possibly in genetically predisposed patients, responsible for arthritis at times similar to rheumatoid arthritis (15). Hsu et al. (16) argued in 2003 against the potential role for HCV in the etiology of RA in a US population aged 60 years and older. Patients with HCV-related arthritis seldom respond to antiinflammatory medications, and although there are no controlled trials to address this issue, it has been recommended to treat these patients with combination antiviral therapy of interferon and ribavirin (17).

Chronic HCV infection was determined by the presence of viral RNA in serum. Autoimmunity is greater in chronic hepatitis C than in chronic hepatitis B. We believe that hepatitis C virus (HCV) infection enhances the initiation and perpetuation of autoimmunity in susceptible individuals (10, 18).

Studies of molecular autoantigens and autoepitopes have begun to define the differences of the B-cell response in autoimmune diseases and virus-associated autoimmunity (19, 20). This provides data that may contribute to the safe application of therapeutic strategies as different as immunosuppression and interferonalpha (IFN-alpha) (13).

HCV infection seems to be, possibly in genetically predisposed patients, responsible for arthritis at times similar to rheumatoid arthritis (15). The occurrence of AKA in patients with RA was first described in

1989. AKA actually recognise three new proteins of rat oesophagus epithelium distinct from sytokeratins. The joins involved in HCV-related arthritis are similar to those in rheumatoid arthritis (RA). This sometimes makes it difficult to differentiate true RA from HCV patients with positive rheumatoid factor but without RA. HCV-related arthritis is usually non-deforming and there are no bony erosions in the joints. HCV-related arthritis commonly presents itself as symmetrical inflammatory arthritis involving small joints (21).

Conclusion

Antikeratin antibodies are a useful marker in differentiating patients with RA from those with hepatitis C arthritis.

KLINIČKI ZNAČAJ ANTIKERATIN ANTITELA U REUMATOIDNOM I SIMETRIČNOM POLIARTRITISU PRAĆENOM HEPATITIS C INFEKCIJOM

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Kratak sadržaj: Hronični hepatitis C virus (HCV) je povezan sa ekstrahepatičnim autoimunim fenomenima. Kod ovih pacijenata nalazi se niz autoantitela. Ovo izučavanje je izvedeno da bi se ispitao klinički značaj antitela u reumatoidnom artritisu (RA) i kod pacijenata sa simetričnim poliartritisom praćenim hepatitis C infekcijom. Serumska antikeratin antitela su ispitivana u tri različite grupe pacijenata koji su bili seropozitivni na reumatoidni faktor (RF). Grupa 1: 31 pacijent sa HCV praćenim simetričnom poliartralgijom ili artritisom. Grupa 2: 28 pacijenata sa RA (modifikovani ACR kriterijumi za verovatni RA). Grupa 3: 16 pacijenata sa autoimunim poremećajima ali ne i sa RA. Sedamnaest zdravih osoba slične starosti i pola služilo je kao kontrolna grupa. U našem proučavanju, 75 pacijenata koji su bili pozitivni na reumatoidni faktor (mereno ELISA tehnikom sa cutoff 40 U/mL) ispitivano je na antikeratin antitela primenom indirektne imunofluorescentne tehnike sa serumskim razblaženjem 1:10. Antikeratinska antitela su detektovane u 18/28 (64%) pacijenata (9%) sa HCV-uslovljenim artritisom ($p>0.0001$). Antikeratinska antitela nisu nađena u serumima zdravih osoba.

Ključne reči: hepatitis C, reumatoidni artritis, simetrični poliartritis, antikeratinska antitela

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