REVIEW ARTICLE

Anti CCP Antibodies in the Diagnosis and Prognosis of Rheumatoid Arthritis

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Introduction

Rheumatoid Arthritis (RA) is a systemic inflammatory disease characterized by chronic and erosive polyarthritis with irreversible joint disability. It is characterized by multiple deformities and is associated with considerable morbidity and mortality (1). Although the precise etiology of RA remains unknown, there is strong evidence for autoimmunity since several autoantibodies are associated with the disease. Besides the rheumatoid factor (RF), another group of autoantibodies has recently been detected in serum of patients with RA patients: the anti-cyclic citrullinated peptide antibodies (anti CCP) (2).

History

Anti perinuclear factor (APF) and anti keratin antibodies (AKA), two tests known for a long time, have a high specificity of up to 70% for RA (3,4). The tests are done by immunofluorescence but did not become popular in clinical practice, despite high specificity, due to various technical difficulties in doing the assays. Filaggrin was identified as the antigen that was targeted by both these autoantibodies.Subsequent studies demonstrated that autoantibodies from RA patients react with a series of different citrullinated antigens , including fibrinogen, deiminated Epstein- Barr Virus Nuclear Antigen 1 and vimentin (5,6,7), which is a member of the intermediate filament family of proteins. Several assays for detecting ACPAs were developed in the following years, employing mutated citrullinated Vimentin (MCV-assay), filaggrin derived peptides (CCP-assay) (8), viral citrullinated peptides (VCP-assay). The first generation of ELISA for anti-CCP (CCP1),using several filaggrin epitopes, had high specificity for RA (>85%) and a sensitivity of 65-70% (2). With 2nd generation anti-CCP assay (CCP2) assays the specificity for RA has increased to 96-98% (9,10). An ELISA made with third generation CCP3 shows 5% greater sensitivity at detecting RA patients than the second generation CCP2, while maintaining a very high specificity.

Role in Pathogenesis

During inflammation,citrulline is incorporated enzymatically into proteins. Citrulline is formed by de-imination of arginine residues in several proteins by the action of enzyme peptidylarginine deiminase (PAD). PAD 2 and PAD 4 isoenzymes are abundant in the inflammatory RA synovium and cause the local citrullination of synovial proteins, such as fibrin. Citrullinated extracellular fibrin in the RA synovium may be one of the major autoantigens driving the local immune response, suggested by the discovery of local production of anti-CCP and anti-citrullinated filaggrin antibodies in the joint (2).

Association of Anti CCP with HLA Shared Epitope

The genetic basis for RA is not fully elucidated. A number of investigators have found an association between anti-CCP antibody production and the presence of certain MHC class II alleles containing the 'shared epitope' (11,12). The shared epitope refers to a conserved motif in the peptide binding cleft of the MHC molecule which is encoded by certain HLA class II alleles, and has been associated with risk of developing RA, as well as greater disease severity. Furthermore, RA patients with both anti-CCP antibodies and shared epitope alleles had more destructive joint disease than RA patients with anti-CCP antibodies and no shared epitope alleles (11). In RA patients shared epitope alleles are strongly associated with anti CCP antibodies. Moreover, more severe disease progression is found in RA patients with both anti-CCP antibodies and shared epitope alleles (13). An interesting recent study has demonstrated a strong gene-environment interaction between cigarette smoking and anti-CCP antibody production in RA patients (14).

Limitations of Rheumatoid Factor (RF)

RF are antibodies directed to the constant region of immunoglobulins of the IgG class and are found in 70-80 % of patients with RA. IgM RF, the isotype most typically detected, is seen not only in RA but also in various other conditions like other autoimmune diseases, infections and in up to 5-10% of healthy individuals (15). The combined detection of IgM and IgA RFs in a serum is a strong indicator of RA (16) . However, IgA RFs are not widely available.

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Clinical Significance of Anti-CCP Antibodies

1. Diagnosis of early RA

The current therapeutic strategy uses increasingly aggressive regimens early in the course of the disease as most of bony damage occurs in first two years in 90% of patients (17). Thus, early diagnosis is crucial. The 1987 American College of Rheumatology (ACR) criteria are rarely met during the first few months of the disease. In many early cases of RA, clinical symptoms are milder and nonspecific and patients will not fulfill ACR classification criteria for RA. Therefore, the detection of a disease specific autoantibody like anti-CCP is important. Anti-CCP antibodies may be detected in roughly 50-60% of patients with early RA usually after 3-6 months of symptoms (18). The specificity of anti-CCP is around 95-98% as regards undifferentiated forms of arthritis that do not develop into RA (19). IgM RF are often found in the same patients, but with much lower specificity for RA. A study using the CCP2 assay found progression from undifferentiated polyarthritis to RA in 93% of anti-CCP positive patients but only in 25% of anti-CCP negative patients after 3 years of follow-up (*Fig. 1*).

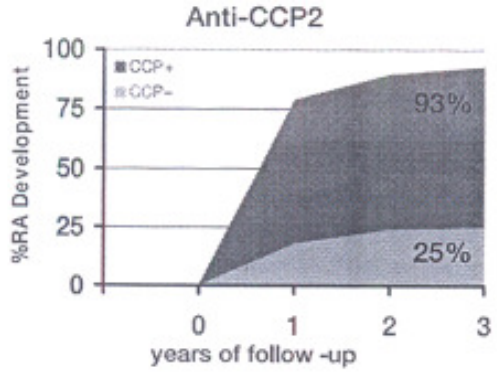

Fig 1. Development of Rheumatoid Arthritis in Patients with Undifferentiated Arthritis, According to the Anti-CCP Antibody Status

2. Correlation with Disease Activity Parameters

Patients with RA show considerable variability in disease activity, which can be difficult to predict at the onset of disease. Anti-CCP antibodies have proven useful in identifying those patients who are likely to have clinically significant disease activity. Several investigators have found that Anti-CCP antibodies were positively correlated with higher erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), swollen joint count, and worse physician global assessment ratings. Presence of rheumatoid factor was positively correlated with increased ESR and CRP, but there was no association with other disease activity markers (20). Thus anti-CCP antibodies identify patients with significantly greater disease activity more reliably than rheumatoid factor.

3. Prediction of Disease Damage

Several observations have indicated that anti-CCP positive early RA patients may develop a more erosive disease than those without anti-CCP (21). Other investigators have confirmed this and suggested the superiority of anti-CCP over IgM RF in predicting an erosive disease course. Anti-CCP has been shown to be an independent predictor of radiological damage and progression (22). The combination of anti-CCP and IgM RF increased the ability to predict erosive and progressive disease (23).

3.Differentiation From other Diseases

In significant number of patients the differential diagnosis between elderly onset rheumatoid arthritis (EORA) and polymyalgia rheumatica (PMR) is very difficult because of the lack of specific serum markers (24). The presence of anti-CCP antibodies in a patient with clinical symptoms of PMR must be interpreted as highly suggestive of EORA. The presence of anti-CCP antibodies may be useful in distinguishing RA from erosive SLE and also helpful in discriminating hepatitis-C-related arthropathy from RA (25).

4.Relationship with Therapeutic Interventions

In a study of 62 patients with refractory RA treated with infliximab, a significant reduction in RF titers was shown during infliximab treatment, whereas anti-CCP antibodies were not modulated. Anti-CCP positive patients usually remain positive despite treatment. This led to the suggestion that that RF and anti CCP antibodies are two different, independent auto-antibody systems in RA (26). Recent study however, indicate that anti-TNF alpha treatment in RA results in a decrease in the serum titers of RF and anti-CCP antibodies in patients showing clinical improvement, suggesting that these measurements may be a useful adjunct in assessing treatment efficacy (27).

Conclusion

Anti-CCP and RF are distinct antibody system, with different diagnostic performance. Anti-CCP antibodies combine high specificity with high sensitivity for RA. They have superior diagnostic performance in early and undifferentiated arthritis. They show a great promise as a diagnostic marker of RA as they can be detected very early in RA and they may predict the eventual development into RA. They have also shown the ability to distinguish between erosive and non erosive disease, making them a good prognostic marker. These antibodies represent an important addition to the diagnostic armamentarium in RA.

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