

Role of anti-citrullinated protein antibodies in diagnosis and prognosis of rheumatoid arthritis

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Abstract

Antibodies to citrullinated proteins/peptides (ACPAs) are the second serological marker to have recently been included in the 2010 ACR/EULAR Rheumatoid Arthritis (RA) Classification Criteria, which are focused on early diagnosis and therapy. This review discusses their history and some clinical aspects of ACPAs, focusing on the diagnostic utility of anti-cyclic citrullinated peptide (anti-CCP) antibodies as a marker of RA as compared to the widely used rheumatoid factor (RF). Simultaneously, this review aims to raise physician awareness and interest in anti-citrullinated vimentin antibody (anti-Sa/anti-MCV), another member of the ACPA family, which appears to have a better predictive value as a marker of RA than anti-CCP or RF and correlates closely with disease activity and therapeutic response among patients with RA.

Key words: antibodies to citrullinated protein/peptide, anti-cyclic citrullinated peptide, anti-mutated citrullinated vimentin, anti-Sa, rheumatoid arthritis, American College of Rheumatology.

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory autoimmune disorder, causing progressive joint destruction as a result of chronic synovitis. In many cases, this systemic disease of unclear etiology leads to a severe disability and a significant deterioration in the quality of life. Its various economic, social and psychological consequences indicate that the prevention, or at least retardation, of irreversible joint damage should be the principal therapeutic aim in RA [1, 2]. Prevention of such damage may be achieved by the very early implementation of aggressive treatments with potentially toxic and expensive drugs [3, 4]. The optimal treatment strategy, which should be started as early as possible and tailored to each individual's expected disease severity, requires access to adequate diagnostic and predictive tools [5, 6].

The 1987 American College of Rheumatology (ACR) criteria for the classification of RA were mainly based on clinical manifestations and included parameters rarely met in early disease [7]. Rheumatoid factor (RF), the presence of which was the only serological 1987 ACR criterion, lacks RA specificity and has a low prevalence in new-onset disease [8-10].

Given the above, it has become necessary to identify other diagnostic and prognostic markers of RA that are characterized by high sensitivity and specificity and are more appropriate for the diagnosis of new-onset disease.

Antibodies against citrullinated proteins/peptides (ACPAs) seem to fulfill these requirements. ACPAs are the second serological marker (apart from RF) to have recently been included in the 2010 ACR/EULAR classification criteria for RA, which are focused on early diagnosis and therapy (Table I) [11]. It is therefore a good occasion to recall the history and summarize some clinical aspects of ACPAs in the diagnosis of RA.

Anti-citrullinated protein antibodies

In 1964 – 24 years after Waaler’s discovery of the first human autoantibody, rheumatoid factor (RF) [12] – Nienhuis *et al.* described other RA-specific autoantibodies and called them the anti-perinuclear factor (APF). It was discovered that APFs bind to the proteins of keratohyalin granules in buccal mucosa cells and result in a perinuclear pattern of fluorescence in an indirect immunofluorescence test. In this crucial study, about 50% of the sera from RA patients were APF-positive, in comparison to only 1% of the sera from a control population [13]. Fifteen years later, the so-called anti-keratin autoantibodies (AKA), specifically present in rheumatoid sera and reacting with the keratinized tissue of animal oesophageal mucosa, were described by Young *et al.* [14].

In 1993, the acidic/neutral isoform of filaggrin, an intermediate filament-associated protein (IFAP), was reported to be recognized by RA-specific autoantibodies [15]. When it was shown that both APF and AKA react with human epidermal filaggrin and (pro)filaggrin-related proteins, they were jointly named anti-filaggrin autoantibodies (AFA) [16]. Filaggrin is expressed as profilaggrin – a high-molecular-weight insoluble precursor stored in the so-called keratohyalin granules – during the terminal differentiation of the mammalian epidermis [17]. After the granules’ dispersion, profilaggrin undergoes a specific dephosphorylation and proteolytic cleavage to release the soluble filaggrin. Eventually, the calcium-dependent enzyme peptidylarginine deiminase (PAD) catalyzes the conversion of arginine residues to citrulline residues in filaggrin [18]. This post-transcriptional modification, known as citrullination or deimination, generates citrulline – the amino acid that has been described as the major component of antigenic determinants recognized by RA-specific autoantibodies [19]. Subsequent experiments using human recombinant filaggrin have revealed that only the citrullinated protein can specifically react with AFA; its non-citrullinated form cannot [20].

Table I. From the 2010 ACR/EULAR classification criteria for rheumatoid arthritis [11]

Target population (Who should be tested?): Patients who: 1. Have at least 1 joint with definite clinical synovitis (swelling). 2. With the synovitis not better explained by another disease.	Score
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)**	
Negative RF <i>and</i> negative ACPA	0
Low-positive RF <i>or</i> low-positive ACPA	2
High-positive RF <i>or</i> high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP <i>and</i> normal ESR	0
Abnormal CRP <i>or</i> abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

**Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are > 3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA – anti-citrullinated protein antibody

More recently, it has been reported that deiminated (pro)filaggrin, the supposed target of AFA, is not expressed by articular tissues. This filament-associated protein is probably a cross-reactive autoantigen, not involved in RA [21]. As a result, AFAs have been renamed anti-citrullinated protein antibodies (ACPAs).

In order to define the potential targets for ACPAs, numerous studies have been focused on the detection and identification of deiminated proteins present in rheumatoid tissues. Of special interest are fibrin [22], vimentin [23], fibronectin [24], Epstein-Barr nuclear antigen 1 (EBNA-1) [25], α -enolase [26], collagen type I [27], collagen type II [28] and histones [29]. The synovial "citrullinome" is a new term describing the entire set of citrullinated proteins in the inflamed synovium [30].

The isotypes of PAD are localized within the cell as inactive forms of the enzyme. Normal living cells do not contain the relatively high levels of calcium (Ca^{2+}) necessary for the activation of PADs. In the case of dying cells, the disintegration of the plasma membrane and organelle membranes causes a strong increase in Ca^{2+} concentration as a result of extracellular Ca^{2+} influx and Ca^{2+} liberation from intracellular stores. This Ca^{2+} increase can lead to the activation of PADs and eventual citrullination of various proteins. Peptidylarginine deiminases released from the dying cells may also be activated by extracellular Ca^{2+} [31]. When large-scale cell death occurs, e.g. during inflammation, clearance mechanisms may not be in a position to effectively remove apoptotic remnants. Consequently, the citrullinated proteins come into contact with immune system cells and may initiate the ACPA response. As the presence of deiminated proteins has been demonstrated in a variety of inflammatory conditions, citrullination is widely accepted as a common process associated with inflammation and is non-specific for RA. Therefore, high RA specificity of ACPAs appears to be a result of an abnormal antibody response to citrullinated proteins, which is specific for RA, and most probably depends on the patient's genetic background and environmental risk factors [32, 33].

Clinical aspects

Along with investigations into the possible role of ACPA response in RA pathogenesis, efforts have also been focused on designing serological tests that could become clinically available for measuring ACPAs. Filaggrin extracted from human epidermis [34] and *in vitro* citrullinated recombinant filaggrin [20] were primarily used as antigens in enzyme-linked immunosorbent assays (ELISAs), but they did not provide adequate standardization due to their heterogeneity. Schellekens *et al.* designed a synthetic cyclic citrullinated peptide (CCP) and used it

as a new antigenic substrate in anti-CCP ELISA to detect ACPAs [35]. Van Venrooij *et al.* developed a second generation of the test, known as anti-CCP2 ELISA, which demonstrates a higher sensitivity for RA than anti-CCP1 and is still the most commonly used test for ACPAs in clinical practice [36]. The anti-mutated citrullinated vimentin (Anti-MCV) ELISA using MCV as the antigenic substrate has been developed to improve detection of the antibody against citrullinated vimentin (anti-Sa), a particular member of the ACPA family of antibodies [37]. Citrullinated vimentin appears to be one of the synovial deiminated autoantigens generated during apoptosis [23].

Rheumatoid factor, commonly regarded as the serological hallmark of RA, may be present in a variety of other rheumatic and non-rheumatic conditions, and also among healthy individuals [8]. In contrast with RF, anti-CCP antibodies have a well-documented high specificity for RA. Van Venrooij *et al.* have accumulated anti-CCP2 test results from 144 independent studies related to RA (published between 2002 and 2008) and prepared an overview of the test's diagnostic value [38]. The specificity of anti-CCP2 vs. normal controls was 99%, whereas specificity vs. disease non-RA controls was 94.2%. The sensitivity for established RA was 75.2% compared with 61% for early disease. It has been widely observed and accepted that an anti-CCP diagnostic test provides higher RA specificity than IgM-RF, and similar or slightly lower sensitivity in comparison to RF [38, 39]. Since multiple different methods and cut-off values are commonly used for the determination of RF and its significance, individual studies can be difficult to compare [40]. By contrast, increasing standardization of ACPA measurement was emphasized in the 2010 RA Classification Criteria. The authors suggested that increasingly significant differences in the standardization of ACPA and RF testing may be taken into consideration in further amendments of these criteria [11].

In RF-negative RA patients, the anti-CCP2 test demonstrates sensitivity ranging from about 35% to 80% and specificity over 90% vs. non-RA disease controls [40-43]. Anti-CCP antibodies are associated with a poor prognosis in terms of radiographic joint damage and functional outcomes in patients with seronegative RA and also in recent-onset RA [41-44]. In addition, anti-CCP may be a predictive marker of disease progression to RA in patients with early undifferentiated arthritis (UA) [45]. Thus, anti-CCP2 testing may be helpful in making individualized treatment decisions regarding the early implementation of disease-modifying anti-rheumatic drugs (DMARDs) in patients with new-onset UA [46]. Chibnick *et al.* observed a strong correlation between a higher titer of anti-CCP and

shorter time to diagnosis of RA [47]. A steady increase of anti-CCP levels prior to disease onset is probably associated with both quantitative and qualitative changes of ACPA response during the development of RA. Ioan-Facsinay *et al.* analyzed sera from 81 RA patients, 195 of their unaffected relatives (mainly first-degree), and 91 unrelated control subjects to qualitatively characterize ACPA response in health and disease [48]. Anti-CCP was present in about 91% of RA patients, 19% of their healthy relatives and 9% of healthy controls. Interestingly, anti-Sa antibodies were found with a prevalence of 61% in anti-CCP-positive RA patients and 0% in anti-CCP-positive healthy relatives. Moreover, the expression of anti-CCP immunoglobulin isotypes among RA patients was more extensive (1-6 isotypes) in comparison to healthy anti-CCP-positive relatives (1-2 isotypes).

Detection of anti-MCV antibodies has been shown to provide a sensitivity of 62-84% and specificity of 83-95% for the diagnosis of RA. Considering these parameters, anti-MCV ELISA seems to have a comparable diagnostic value in RA to that of the anti-CCP2 assay [49-53]. Many authors suggest that anti-MCV/anti-Sa antibodies are a better predictive marker of subsequent high RA severity and radiographic joint damage than anti-CCP2 or RF [54-57]. Since some researchers do not agree with the additional significance of this test in the diagnosis and prognosis of RA, further investigations among different populations and different groups of patients are required [53, 58, 59]. In contrast with anti-CCP, anti-MCV/anti-Sa titers seem to correlate closely with disease activity and therapeutic response in patients with RA [55]. Therefore, the clinical value of the anti-MCV/anti-Sa test has become a promising research objective.

Conclusions

The 2010 ACR/EULAR classification criteria for RA give official confirmation for the use of ACPA testing in the diagnosis of RA [11]. Interestingly, both serological markers (RF and ACPAs) are scored equally in these criteria. In light of how recent many of these studies are, one can regard this approach as a kind of scientific caution. One can expect that the well-documented diagnostic and prognostic significance of ACPAs, higher than that of the RF, will soon be formally endorsed, especially with regards to RA of recent onset and UA.

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