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# **EDITORIAL**

## CLINICAL INTEREST OF AUTOANTIBODIES DIRECTED AGAINST CITRULLINATED PEPTIDES IN INDIAN PATIENTS WITH RHEUMATOID ARTHRITIS

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An early diagnosis of rheumatoid arthritis (RA) is crucial in order to begin the most appropriate and effective therapies to prevent definitive structural damage and obtain a sustained remission of the disease.

### ANTI-CCP AS A DIAGNOSIS MARKER

The assays detecting the autoantibodies directed against citrullinated peptides (ACPA) are the main diagnosis tools of this autoimmune disease. Rheumatoid factor (RF) is still widely used but it is not specific for the diagnosis of RA as it can be found in others autoimmune or infectious (septic endocarditis, viral hepatitis...) diseases.<sup>[1]</sup> ACPA may be detected in healthy individuals, months or even years before the onset of clinical RA. Linear (human citrullinated fibrinogen or deiminated recombinant rat filaggrin) or cyclic citrullinated peptides are in the basis of several types of assays that identify the presence of ACPA.<sup>[2]</sup> However, the first and second generation of anti-cyclic citrullinated peptides (anti-CCP1 and 2) tests are the most documented assays in the literature. According to different studies,[3] the sensitivity and specificity of anti-CCP1 tests thus vary from 44 to 56% and from 90 to 98% respectively, whereas performances of anti-CCP2 are logically better and range from 64 to 89% and from 88 to 99% respectively. The specificity of the anti-CCP tests is therefore not exclusive to BA since anti-CCP could be detected during Lyme's disease, hepatitis C infection, psoriatic arthritis, multiple sclerosis and primary Sjogren's syndrome.<sup>[1]</sup> In this issue of the Indian Journal of Medical Science, Rajiva Gupta and coll. [4] confirm the interest of anti-CCP2 antibodies for the diagnosis of RA in Indian patients. They assessed the results of anti-CCP2 test in 63 Indian patients with RA and 51 patients with non-RA rheumatic diseases with joint pain. Similar to others studies,[3] the authors showed that anti-CCP2

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assay has a sensitivity of 85% and a specificity of 90% for RA. These results are important to confirm that the autoimmune response of RA in the Indian population also mainly targets citrullinated antigens.

## ANTI-CCP AS A MARKER OF RHEUMATOID ARTHRITIS SEVERITY

The positivity of anti-CCP tests is also a marker of the erosive forms of RA. Anti-CCP1 positivity at the onset of the disease has been shown to predict RA structural damage after 6 years of evolution.<sup>[5]</sup> Furthermore, in case of initial negativity, a sequential assessment of anti-CCP2 antibodies is required since their positivity during the first 3 years of RA evolution is associated with further higher destruction of the joints.[6] In the study of Rajiva Gupta and coll., the radiographs of hands and feet showed erosions in 50.8% of the patients. However, the mean titers of anti-CCP2 antibody in the erosive and non-erosive group of RA patients were comparable (69.4 vs 68.9 units, P=0.9). Anti-CCP2 antibodies alone were not associated with structural damage whereas 56% of RA patients who were both anti-CCP2 and IgM RF positive had significantly more erosion (P=0.01) than anti-CCP2+ IgM RF- patients. This highlights the importance of the concomitant assessment of both RF and anti-CCP2 antibodies in early RA patients in order to predict the forms likely to be associated with structural damage. These patients should benefit from a closer followup and are candidate for early and intensive treatment.

The association of anti-CCP positivity with extra-articular features of RA is

described.<sup>[7]</sup> Gupta *and coll.* observed sicca symptoms and peripheral neuropathy in 11 and 16% of the patients respectively. None of them had interstitial lung disease, vasculitis, rheumatoid nodule, Raynaud's phenomenon, scleritis or lymphadenopathy. This relatively weak number of extra-articular manifestations of the RA patients followed-up in this study might thus explain the absence of association between them and the anti-CCP status. A longer follow-up of the patients will help to clarify this point.

#### **FUTURE PROSPECTS**

# Anti-CCP as a marker of the efficacy of treatment

Anti-CCP levels may be correlated to the response of therapy, notably to anti-TNF drugs. A decrease in both autoimmune (anti-CCP and IgM RF) and inflammatory (erythrocyte sedimentation rate, C-reactive protein) markers has been shown in patients treated with adalimumab and considered as good responders according to the European league against rheumatism (EULAR) criteria.<sup>[8]</sup> Similar results were described with other anti-TNF drugs (infliximab and etanercept) and anti-CD20 (rituximab). Prospective studies in Indian RA patients treated with biologics may be useful to confirm that anti-CCP titers decrease in accordance with good clinical response to treatment

#### Improvement of the current anti-CCP tests

The autoimmune response of RA is known to target several citrullinated proteins such as the vimentin -an intermediate filament abundantly expressed in synovial fibroblastsand EBNA-1, a protein of the Epstein-Barr virus. Using a proteomic analysis, we have recently shown that citrullinated glycolytic enzymes and molecular chaperones may represent candidate autoantigens in RA.<sup>[9]</sup> The discovery of new citrullinated RA autoantigens will allow to enhance the sensitivity of current RA diagnostic tests. We thus have shown in a cohort of patients with very early arthritis that a citrullinated peptide derived from the far upstream element-binding proteins (FUSE-BP) may enhance the diagnosis value of current anti-CCP2 tests. The development and evaluation of these new diagnosis tests will require independent cohort of patients to confirm their promises.

### CONCLUSION

Rajiva Gupta *and colleagues* showed that anti-CCP antibodies have high sensitivity and specificity for the diagnosis of RA in Indian patients. This interesting work constitutes another plea for a revision of the current American College of Rheumatology (ACR) criteria for RA diagnosis that, to date, include the positivity of RF but not of anti-CCP, despite their superiority.

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