Diagnostic Utility of Anticarbamylated Protein Antibodies as Measured Using Carbamylated Fetal Calf Serum

To the Editor:

Rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) are important biomarkers in the diagnosis of rheumatoid arthritis (RA), but leave a gap of about 30–50% seronegative RA, which drives the demand for novel biomarkers. In 2011 a novel autoantibody system, anticarbamylated protein (anti-CarP) antibodies, was described in the sera of patients with RA.1 In contrast to enzyme-mediated protein citrullination, carbamylation is a chemical reaction whereby cyanoate converts lysine into homocitrulline1, a protein modification that is chemically similar to citrulline (1 CH2 longer side chain)2. Most studies on anti-CarP antibodies have used an ELISA based on carbamylated fetal calf serum (Ca-FCS) and accordingly a complex mixture of carbamylated proteins as the antigen(s)1-2. Although many clinical observations have been reported, precise information on the antigenic targets of anti-CarP antibodies is limited. Importantly, anti-CarP antibodies have been detected in both ACPA-positive and ACPA-negative RA patients, suggesting that they might represent an important test in the diagnosis of RA1,2. A recent metaanalysis estimated the sensitivity, specificity, and OR of anti-CarP antibodies as 42% (95% CI 38–45), 96% (95% CI 95–97), and 17 (95% CI 12–24), respectively, when comparing RA to healthy controls3. It was also demonstrated that anti-CarP antibodies predict joint damage as assessed by total Sharp/van der Heijde score in a large cohort of sequential RA samples1,3,2. Additionally, anti-CarP antibodies were reported to be useful in predicting the future development of RA in patients presenting with arthralgia, in first-degree relatives of patients with RA, and even in apparently healthy individuals3. Besides the potential utility in the diagnosis of RA, one of the main benefits of anti-CarP antibodies is the reported strong association with joint erosions and more rapid radiographic progression of disease1,3. Even though anti-CarP antibodies are predominantly found in patients with RA, they are also found in other inflammatory conditions, albeit at considerably lower frequencies4, which certainly brings into question the diagnostic specificity.

In this context, we read with interest the recent paper by Nakabo, et al5 who reported strong association with joint erosions and more rapid radiographic progression of disease. This is of particular importance because of the attempt to identify patients with RA as early as possible, ideally in the preclinical phase of the disease.

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Figure 1. OR for rheumatoid arthritis (RA) for rheumatoid factor (RF) and anticitrullinated protein/peptide antibodies (ACPA) with and without anticarbamylated protein (anti-CarP) antibodies. Adding anti-CarP antibodies to the combination of RF and ACPA (as used in the classification criteria) increased the OR 3-fold from 36.7 to 112.2 (p = 0.04). Data derived from Shi, et al4. 95% CI are used as error bars. CCP: cyclic citrullinated peptide.
Dr. Mahler is listed among inventors on a patent application on the detection of anti-CarP antibodies in RA. Dr. Fritzler is a consultant and has received honoraria from Inova Diagnostics Inc. and gifts in kind from Euroimmun GmbH.

REFERENCES


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