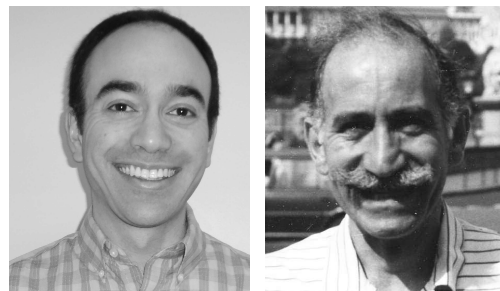Editorial

Palindromic Rheumatism: A Pre-Rheumatoid Arthritis State?

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease that can be debilitating if left untreated, and has demonstrated increased mortality[1]. With each passing year, the rheumatology community better understands how to effectively treat and manage these patients, and complete remission is possible. However, remission is often achieved using at least one, if not a combination of, disease-modifying agents, not to mention glucocorticoids, which many patients are initially resistant to, and which can cause significant side effects and have poor connotation. Over the last decade, rheumatologists have seen the importance of new treatment interventions, achieving improved outcomes for the RA patient community through more aggressive and earlier therapeutic management, as well as many new pharmacologic treatment options.

Despite these important advances in the field, we still lack strong predictive measures for RA at most stages of disease. Which patients will respond better to which disease-modifying agents or biologics? Which patients are more likely to develop permanent bone changes? Who will most benefit from early intervention? Can we predict who will develop RA at all?

Data are lacking on this last, and possibly most important, question: If we could reliably predict future RA in most, if not all patients, perhaps we could treat less aggressively using safer methods with more successful and consistently positive outcomes. There are 3 groups of patients where this could be assessed: undifferentiated arthritis — those positive for anticitrullinated protein antibodies (ACPA) with arthralgia but no discernible arthritis — and those with palindromic rheumatism (PR). PR is clinically characterized by intermittent flares of acute arthritis often involving only one joint per flare[2]. A correlation has also been well documented in previous studies between PR and RA, with many patients developing RA some time after a diagnosis of PR[3]. As RA is a common disorder, a biomarker to predict this progression would be invaluable to allow physicians to more intensively monitor and treat those predicted to develop RA.

In this issue of *The Journal*, Sanmartí and colleagues look at this question with a focus on ACPA as their biomarker of choice[4]. They identified 71 patients at their center with a diagnosis of PR and at least one ACPA test result available. These patients were followed for an average of 12 years for the possible evolution from PR to RA, and then were stratified by their ACPA status. Sixteen patients developed RA, with a further 8 developing other rheumatic diseases, half of whom were diagnosed with systemic lupus erythematosus. Of the 16 patients who developed RA, 11 were ACPA-positive, while 26 of 47 of those who did not develop RA were also ACPA-positive. This was associated with sensitivity for ACPA for predicting conversion from PR to RA of 68.75% and specificity of 52.73%. Sanmartí and colleagues identified a nonsignificant trend suggesting a positive ACPA favors development of RA, but concluded ACPA is likely not a valuable biomarker to predict a transition from PR to RA.

These results contradict an earlier study at our center, which had a similar-size cohort of 61 patients with PR, of whom 29 developed RA[5]. Twenty-four of 29 patients who developed RA were ACPA-positive, while 10 of the remaining 32 patients also were ACPA-positive. The reported sensitivity was higher, at 83%, with a specificity of 68%. A second study reported in 2010 from a smaller Japanese cohort found similar results[6], with 11 of 28 patients with PR developing RA. Ten of the 11 were ACPA-positive, with only 3 of 17 remaining patients also positive.

Why might this difference exist? As Sanmartí and colleagues suggest, the timing of the ACPA measurement may play an important role, as ACPA status was determined on average earlier in the disease course in our local cohort, 1 year, and the Japanese cohort, at initial presentation, compared to 5 years in the Sanmartí cohort. This may have created a selection bias, as those with longer-standing stable

disease may be less likely to transform to RA. This suggests that ACPA may have a predictive role earlier rather than later in patients with PR, although it was disappointing for its overall performance.

Further, three-quarters of the patients in the present study were treated with hydroxychloroquine, an agent that is well known in the treatment of both PR and RA. While not reported in our local study originally, many patients who had been treated had stopped antimalarials when the disease appeared quiescent, and only reappeared for followup after progression to RA. This different treatment approach may also explain the disparity in ACPA performance, as one might expect to see less progression to RA in patients on treatment than not. In other words, hydroxychloroquine use may prevent the transition to RA[7].

Sanmartí's study lends further evidence that ACPA is commonly present in patients with PR. In the end, their study questions whether or not ACPA can also be used to predict RA transformation. If predictive, physicians gain a valuable tool to aggressively combat RA at its earliest stages, and can confidently know they are preventing future disease. If not, it cautions physicians that, in fact, a positive ACPA is not a guaranteed diagnosis of RA, and a proper history and physical examination must be pursued as usual. It also emphasizes to the rheumatology community the need to continue the search for that magic bullet that will lead to the early successful diagnosis and treatment of all patients with RA.

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