Association of antinucleosome antibodies with disease flare in serologically active clinically quiescent patients with SLE

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Evaluation of: Ng KP, Manson JJ, Rahman A, Isenberg DA: Association of antinucleosome antibodies with disease flare in serologically active clinically quiescent patients with systemic lupus erythematosus. *Arthritis Rheum.* 55(6), 900–904 (2006). Clinical laboratory correlations in systemic lupus erythematosus (SLE) have been used in a number of different approaches. A number of autoantibodies are typically present many years before the SLE diagnosis. Autoantibodies are also two of 11 American College of Rheumatology classification criteria for SLE. In terms of prognosis studies, anti-DNA antibodies and depressed levels of complement are associated with active lupus and, specifically, active nephritis. It is in this area of association of clinically active disease with serologic abnormalities that discordance may also occur. This usually takes the form of serologic activity and clinical quiescence (SACQ). Ng and colleagues address this issue of serologic and clinical discordance and introduce an additional antibody, antinucleosome antibody, to better predict subsequent flares. Although not all of these patients were truly SACQ, the authors have added an additional potential laboratory marker of flare. These studies must now be confirmed in other cohorts.

This article will review the recent analysis by Ng and colleagues of systemic lupus erythematosus (SLE) and its associated effects [1]. Since the initial descriptions of the lupus erythematosus cell phenomenon, the fluorescent antinuclear antibody test and, subsequently, the anti-double-stranded (ds)DNA antibody test and assays of serum complement levels for use in SLE, clinical researchers have described clinical laboratory correlations. These associations have been used in a number of different approaches: predicting the development of clinical disease [2,3], association with the diagnosis of the disease [4] and predicting prognosis of the disease [5–9]. In this latter approach, the serologic activity may be associated with disease activity and may predict disease flare, the type of disease flare or the response to treatment. It is of interest to highlight these different clinical laboratory associations to better understand the contribution of Ng and colleagues.

In 2003, in an important paper in the *New England Journal of Medicine*, Arbuckle and colleagues made a seminal observation on the development of SLE autoantibodies before the diagnosis of the disease, while patients were still asymptomatic [3]. This group investigated stored sera from the Department of Defense Serum Repository containing approximately 30 million specimens collected prospectively from more than 5 million US Armed Forces personnel. From among that entire group, 130 persons were subsequently diagnosed with SLE and their prior sera were available for analysis. The investigators were able to demonstrate that a number of autoantibodies were present before the diagnosis of SLE, including antinuclear antibodies in 78%, anti-Ro antibodies in 47%, anti-La antibodies in 34%, antiphospholipid antibodies in 18%, anti-dsDNA antibodies in 55%, anti-Sm antibodies in 32% and antiribonucleoprotein antibodies in 26%. Antinuclear, antiphospholipid, anti-Ro and anti-La antibodies were present earlier than anti-Sm and antiribonucleoprotein antibodies (a mean of 3.4 versus 1.2 years before diagnosis). Anti-dsDNA antibodies were present at a mean of 2.2 years before diagnosis. Furthermore, in that sample in many patients the earliest available serum was positive and, therefore, the length of time that the antibody may have been positive could have been significantly longer.

Thus, the conclusions were that a number of autoantibodies are typically present many years before the diagnosis of SLE and that the different antibodies appear at differential rates prior to the diagnosis. This lends some credence to the notion that the autoantibodies may somehow be associated with the disease pathogenesis. The implication is that if asymptomatic patients are screened, serologic studies may be positive but should not necessarily lead to treatment, as clinical manifestations may not appear until some years in the future.

Autoantibodies associated with the diagnosis of systemic lupus are in fact hallmarks of this disease. Thus, two of the 11 1982 [10] and 1997 [11] American College of Rheumatology classification criteria are specifically allocated for the presence

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of autoantibodies. These include an antinuclear, anti-DNA or anti-Sm antibody, or antiphospholipid antibodies. Additional criteria of hematologic disorders are also often associated with specific autoantibodies, including Coombs', lymphocytotoxic and antiplatelet antibodies.

In terms of prognosis studies, it has been frequently demonstrated that anti-DNA antibodies and depressed levels of complement, either total hemolytic complement or C3 and C4 components, are associated with active lupus and specifically active renal disease [5–9]. When these serologic abnormalities exist they can be used as markers to follow response of the disease to treatments. However, it is in this area of association of clinically active disease with serologic abnormalities that discordance in the clinical serologic correlations may also occur. This can take the form of serologic activity and clinical quiescence (SACQ) on the one hand or clinical activity and serologic quiescence on the other. We originally described a group of 14 patients, from among 180 patients being followed, who had persistently abnormal serology without overt clinical activity [12]. This SACQ state persisted over a mean of 4 years, during which these patients were untreated. A follow-up 15 years later revealed that seven patients remained clinically well and treatment free while four developed flares, but only after a mean of 5.5 years from the first diagnosis of SACQ [13]. Three patients were lost to follow-up. We later reported that among 609 patients with lupus followed prospectively, 106 had periods of SACQ [14]. These patients were followed over a course of 1 year. During that year, 46 periods of SACQ went on to a clinical flare while 60 did not. There were no predictive factors for flare found in either the SACQ period or the period preceding the SACQ. Since more than half of the patients did not flare over a period of a year, it was concluded that patients with lupus who are SACQ should be followed over time and treated only on the basis of clinical criteria. In a study of remission in SLE, we found that 102 of 703 patients (14.5%) had no clinical activity after receiving no therapy for 1 year, and eight of these patients retained total clinical quiescence with serologic activity for a period of 5 years [15].

In the reverse situation, clinical activity with no classic serologic changes, such as high anti-DNA antibody or low complement levels, occurred in 12% of our patients who had been followed over a period of 5 years. Of these patients, 15% have prolonged periods of clinical activity and serologic quiescence (more than 3 years) [16].

The lack of a correlation between clinical activity and serologic abnormalities may be due to the nature of the assay for the serologic tests. A recent study has demonstrated that there is a low level of agreement between the Farr and enzyme-linked immunosorbent assay techniques for the detection of anti-dsDNA antibody and that the Farr assay correlates better with measures of disease activity [17]. Most of the current therapeutic studies in systemic lupus use the Farr assay to measure their anti-DNA antibody levels.

From the earliest period of the introduction of assays for anti-DNA antibodies, there have been many studies showing the predictive ability of anti-DNA antibody levels for subsequent flares, especially flares of renal disease. Many studies have used these antibody levels to diagnose and treat active lupus, especially active lupus nephritis. However, as indicated above, there are many studies of discordance between anti-DNA antibody levels and clinical disease and, thus, one must assume that some patients are receiving unnecessary therapies for periods of time in the absence of clinical disease. In two studies, Esdaile and colleagues were able to show that fluctuations in laboratory tests are poor predictors of disease exacerbations in SLE [18,19]. Van den Burg and colleagues also recently demonstrated that past presence of anti-DNA antibody levels was not adequate to predict disease flares late in the course of the disease [20]. Finally, a recent study by Tseng and colleagues demonstrated that in a subset of clinically stable lupus patients who had high levels of anti-DNA antibody and elevated C3a complement component, short-term corticosteroid therapy may have averted a subsequent flare [21]. These preliminary results merit further studies for confirmation.

The current study by Ng and colleagues addresses this issue of SACQ, and introduces an additional antibody, antinucleosome antibody, which may better predict subsequent flares in these patients.

In their paper, Ng and colleagues identified 27 of 290 patients (9%) who were SACQ for 6 months. This was defined as a British Isles Lupus Assessment Group (BILAG) of less than 6. A total of 17 of the 27 patients (81%) experienced a flare in the next 5 years, with a median duration to flare of 15 months.

Anti-DNA antibodies predicted flares only if the titers in these patients were five-times above the normal limit. Thus, in patients with elevations less than five-times normal, anti-DNA was not a predictor of flares. However, antinucleosome

antibodies and high titer antinucleosome antibodies were better predictors of time to first flare. The authors conclude that antinucleosome antibodies may be better predictors for future flares than anti-DNA antibodies in patients who are SACQ.

Patients described as SACQ in this paper were still on prednisone and some were on immunosuppressive agents, suggesting that they had residual active disease requiring treatment. The definition of SACQ in this study included clinical quiescence defined as a BILAG value of less than 6. However, this might imply that a patient could present with BILAG scores of one catagory B and two catagory Cs (for a numeric total of 5), which is certainly not clinically quiescent. These patients would not likely have a Systemic Lupus Erythematosus Dsease Activity Index 2000 (SLEDAI-2K) of 0.

Thus, these results should be interpreted as showing that antinucleosome antibody titers are predictive of flares in patients with low-grade lupus disease activity rather than clinically quiescent disease.

Even with this caveat, the authors have added an additional potential laboratory marker of flare in patients with anti-DNA antibodies and minimal clinical activity. There did not appear to be a specific organ flare predicted by these antibodies.

These studies must be confirmed in other cohorts and also in individual patients followed longitudinally as they proceed from remission to serologic activity to clinical flare and then back to remission. Only after such studies will one be able to confirm the predictive ability of antinucleosome antibodies for future flares.

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