Drs. Rasmussen and Scofield reply

To the Editor:

Cafaro and colleagues¹ have studied focus score (FS)–negative (that is, < 1 focus of ≥ 50 lymphocytes per 4 mm²) to FS-positive (≥ 1 focus per 4 mm²) Sjögren syndrome (SS) patients² in a manner similar to our recent study³. As in our study, there was evidence of B cell hyperreactivity among those subjects with a positive minor salivary gland biopsy, although the details of this finding varied between the 2 studies. We found statistically significant elevations of anti-La/SSB and hypergammaglobulinemia, whereas Cafaro, *et al*¹ found numerically increased anti-La/SSB and a statistically increased rheumatoid factor; the latter did not withstand correction for multiple comparisons, however.

We agree that highly sensitive autoantibody detection methods may find low-level, low-titer antibodies, the clinical significance of which is unknown⁴. However, we point out that we only classified our subjects and did not diagnose them. Research classification relies on a set of criteria, whereas diagnosis remains a clinical enterprise for which the gold standard is expert opinion⁵. In addition, our study was at the initial evaluation of the patients, while the studies of Cafaro, *et al*¹, and Carubbi and Alunno⁶ were retrospective. This difference in study design may produce variation in findings.

Also, Cafaro, *et al*¹ found a higher incidence of leukopenia, which is associated with the presence of anti-Ro/SSA⁴, among the FS ≥ 1 subjects compared to those with FS < 1. Of course, as in our study, all these subjects had anti-Ro/SSA⁶. Cafaro and colleagues¹ make the interesting point that their finding of leukopenia fits well with our finding of an increased incidence of an interferon (IFN) signature in the peripheral blood cells of participants with FS ≥ 1 compared to the FS = 0 subjects; this is because leukopenia has been associated with IFN activity and higher FS. We did not find this same association with low white blood cell counts. Perhaps, differences in study design (cross-sectional at diagnosis vs longitudinal), method of autoantibody detection, diagnosis versus classification, and/or cohort size led to this difference.

The pathogenesis of SS is poorly understood. As we stated in our study³ and is again demonstrated in the data of both Cafaro, *et al*¹ and Carubbi and Alunno⁶, the study of FS-negative subjects may allow dissection of the pathogenic associations of T cell pathology (glandular infiltrate), B cell pathology (circulating autoantibodies), and innate immune pathology (IFN activity), as well as clinical manifestations of the disease.

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