Dr. Tebo, *et al,* reply

To the Editor:

We read with great interest the response by Drs. Jearn and Kim[1] to our letter "Presence of Anti-topoisomerase I Antibody Alone May Not Be Sufficient for the Diagnosis of Systemic Sclerosis"[2]. We agree with Drs. Jearn and Kim that the antinuclear antibody (ANA)-negative accompanied by antitopoisomerase I antibody (anti-topo I) positivity is not sufficient to diagnose systemic sclerosis (SSc). Although we noted an apparent association between relatively lower anti-topo I antibody levels (median 76 AU/ml, range 42–118 AU/ml) and lung pathology in ANA-negative (6/11) or -positive (5/11) cases, we only suggested that our observation warrants further study. We did not state that the finding is clinically significant or that this pattern predicts pulmonary epithelial damage.

Our article was written to inform clinicians on practical clues in the interpretation of anti-topo I antibody results in routine clinical settings based on experience at our academic center. The observation that low anti-topo I antibody levels may be associated with lung pathology, though rare (11/3331, 0.3%), was an incidental finding that warrants further investigation. We believe this was worth mentioning because, in clinical practice, physicians often order this autoantibody test sometimes without ANA for patients presenting with dyspnea.

The anti-topo I antibody (regardless of ANA positivity) is included in the 2013 classification criteria for SSc[3]. Clinicians often refer patients to rheumatology or pulmonary care based on the scenario we mentioned in our study. In the absence of harmonized diagnostic immunoassays for the detection of anti-topo I antibodies, our study highlights the importance of thorough assessment of a patient with physical examination and lung imaging if dyspnea is present, as well as ANA testing by the indirect immunofluorescence antibody (IFA) method. To be clear, the intent of ANA IFA screening to detect anti-topo I antibodies as suggested by the authors[1] is not a common practice in the United States, where IFA patterns are generally reported. While guidance to detect anti-topo I antibody based on ANA IFA pattern has recently been reported, unreliability due to subjectivity in their interpretation and differences in the performance characteristics of commercially available ANA IFA reagents are known limitations[4]. It is very likely that correlation between specific ANA IFA patterns and autoantibody targets (i.e., anti-topo I) is highly dependent on the titer of the antibody, the epitope(s) bound, the type of antigen used in the immunoassay, or the antibody isotype/class or source of HEp-2 substrate[4,5]. Thus, in a real-world setting, the relationship between autoantibody specificity and ANA IFA pattern is not absolute.

We agree with Drs. Jearn and Kim regarding the potential limitations of the multiplex assay for detecting anti-topo I antibodies[1]. However, these are not limited to multiplex methodology as outlined in our letter and have been reviewed elsewhere[5]. Our unpublished data comparing results for anti-topo I antibodies by the Theradiag multiplex bead assay and immunodiffusion (traditional method) using well-characterized US SSc samples (n = 445: 118 anti-topo I antibody-positive by multiplex bead assay vs 119 by immunodiffusion and 318 anti-topo antibody-negative by multiplex bead assay vs 326 by immunodiffusion) showed excellent overall agreement of 98.0%, with sensitivity and specificity relative to immunodiffusion of 99.2% and 97.5%, respectively (data not shown). Of note, the median anti-topo I antibody level in the cohort was estimated at 147 AU/ml, which is comparable to 158 AU/ml observed in the patients with SSc in our letter.

We found that significantly elevated anti-topo I antibody levels are strongly associated with a diagnosis of SSc when the ANA by IFA is positive. Of interest, we noted a possible association between lower anti-topo I antibody levels and lung pathology and suggested that this observation warrants further study. Given the progressive course of SSc, its clinical heterogeneity and high penetrance of lung pathology in anti-topo I antibody–positive patients, this association, if confirmed, could be clinically useful.

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