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American College of Rheumatology/European League Against Rheumatism Sjögren's syndrome classification criteria may not be adequate for extraglandular disease and necessitate defining "seronegative Sjögren's syndrome": comment on the article by Shiboski et al

To the Editor:

The recently published American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for classifying primary Sjögren's syndrome (SS) (1) are based on a scoring system that can be applied to individuals who have a positive response on any of the screening questions or any positive item in the EULAR SS Disease Activity Index questionnaire (2). A patient is classified as having SS if she/he has a score of ≥4 from the classification criteria items. However, similar to previous SS classification criteria sets (3–6), there is an inherent problem: the criteria comprise only glandular manifestations. Most patients with primary SS who need aggressive treatment (immunosuppressive or biologic agents) are those with major organ involvement, and a significant proportion of these patients do not have glandular manifestations severe enough to fulfill the classification criteria. This might be due to symptoms and signs related to major organ involvement leading to earlier diagnosis compared to that in patients with only glandular symptoms. The new classification criteria do not seem to resolve this problem. We suggest that the criteria be modified to allow classification (maybe with fewer item scores) when there is major organ involvement. This would be similar to the ability to classify a patient with lupus renal involvement as having systemic lupus erythematosus (SLE) with fewer items when there is biopsy-proven disease, in the Systemic Lupus International Collaborating Clinics (SLICC) criteria (6,7).

Our second concern is that anti-SSA/Ro is the only immunologic marker in the new ACR/EULAR classification criteria. This is also similar to some of the previous criteria sets (3–6). The result is that a patient with no detectable autoantibodies may be classified as having primary SS. A few reports have used the term "seronegative primary SS," which usually denotes "anti-SSA/SSB negative." In clinical practice, our observation is that the majority of patients with primary SS who are negative for anti-SSA/SSB are positive for rheumatoid factor (RF) or antinuclear antibody (ANA). Therefore, there is an urgent need to define seronegative primary SS. The new, as well as most of the previous, classification criteria sets allow classification of individuals who are triple negative (for SSA/SSB, RF, and ANA) as having primary SS. However, this subgroup is not adequately defined or studied. We suggest that clinical and laboratory findings should be evaluated separately and fulfillment of at least 1 clinical and 1 laboratory criteria component should be required for classification, as in the 2012 SLICC classification criteria for SLE (7).

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Reply

To the Editor:

Drs. Tezcan and colleagues point out that some patients with clinically diagnosed SS, presenting with disease-related extraglandular features and anti-SSA/Ro antibodies (or a positive lip biopsy result) but without overt glandular manifestations (i.e., negative findings on salivary and lacrimal function tests), would not fulfill the new ACR/EULAR criteria for primary SS. Tezcan et al also indicate that, in their experience, these patients are often negative for anti-SSA/Ro antibodies and positive for RF and ANA, which are not included among the items in the new criteria set.

The fact that some patients with a given disorder cannot meet the classification criteria for it is not surprising. Classification criteria are not designed to assess the diagnosis in individual cases, but serve to define groups of patients with a given disease to be included in epidemiologic, clinical, and treatment studies. To be valid, classification criteria should have balanced and sufficiently high sensitivity and specificity to minimize the risk that patients without the disorder may be included in, and patients with clearcut disease may be excluded from, specifically designed studies (1). None of the classification criteria proposed for the different autoimmune rheumatic disorders, including those for SS, cover the entire spectrum of the disorder under consideration. To obtain this (in other words, to have a sensitivity of, or very close to, 100%) may be accompanied by an unacceptable loss of specificity.

The 2016 ACR/EULAR classification criteria for SS were developed using statistical methodology that has been approved by both the ACR and EULAR for this purpose and used to define classification criteria for other rheumatic diseases. Thus, the items selected and included in this criteria set were restricted to those that were most important from the perspective of both clinician expert opinion and statistical performance. From a methodologic point of view, classification criteria are quite distinct from diagnostic criteria. Clinicians should be cautious when adopting classification criteria in clinical practice, since a certain number of patients who do not meet the criteria for a given disorder will nonetheless have the disorder. In such cases, clinicians should adopt the therapeutic approach believed to be potentially beneficial for the patient, using their best clinical skill and independent of satisfaction of classification criteria. As pointed out in our report, the gold standard for the diagnosis of SS remains expert opinion.

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