Comment on: Disease evolution in a long-term follow-up of 104 undifferentiated connective tissue disease patients

Sirs,

Undifferentiated connective tissue disease (UCTD) is a wide-spectrum disorder, and it is controversial whether UCTD represents a distinct clinical entity or the presentation of early definite connective tissue disease (CTD). Therefore, it is important to know what clinical and/or laboratory characteristics of UCTD patients might suggest their evolution into definite CTD. We read with great interest the study by Radin *et al*. on the disease evolution of UCTD (1). It is surprising that 44 patients (44%) developed novel clinical and/or laboratory features and that 21 patients (21%) evolved into definite CTD patients in the long-term follow-up of the study (1). However, we have several questions on their study.

In their study, systemic lupus erythematosus (SLE) was the most common definite CTD that progressed from UCTD. In addition, there was a significantly higher prevalence of anti-Ro/SSA and/or anti-RNP antibodies in the patients who evolved into definite CTD (1). However, it was not detailed what definite CTDs were developed by the UCTD patients with anti-Ro/SSA and/or anti-RNP antibodies (1). Moreover, it was not mentioned whether the anti-Ro/SSA antibodies were anti-Ro60 antibodies and/or anti-Ro52 antibodies (1). Anti-Ro60 antibodies are found mainly in sera of patients with SLE and Sjögren's syndrome, whereas anti-Ro52 antibodies are found in several autoimmune entities and conditions (2). Historically, autoantibodies targeting Ro60 and Ro52 antigens could not be identified separately and both antibodies were known simply as anti-Ro/SSA, while antibodies to Ro60 and Ro52 are associated with different autoimmune processes (2, 3). In a previous study (4), there were no statistically significant differences in the prevalence of evolution into definite CTD among anti-Ro/SSA antibody-positive UCTD patients with both anti-Ro60 and anti-Ro52 antibodies, with only anti-Ro60 antibodies, and with only anti-Ro52 antibodies (p=0.063), although the "only anti-Ro60-positive UCTD patients" tended to have an elevated risk of progression to definite CTD (Table I). Although individuals with only anti-Ro60 antibodies are less frequently observed than those with both anti-Ro52 and anti-Ro60 antibodies, only anti-Ro60 reactivity correlates with SLE (2, 5) and shows a tendency for the development of oral ulcers and the presence of autoantibodies against Sm or nRNP/Sm (2). Nevertheless, the interaction between anti-Ro60 and anti-Ro52 antibodies remains obscure. Recently, a large number of commercially available kits and in-house techniques have been used to detect autoantibodies against anti-Ro/SSA, and anti-Ro60 and anti-Ro52 antibodies tend to be detected separately (2). When discussing anti-Ro/SSA antibodies, we should consider anti-Ro60 and anti-Ro52 antibodies separately.

Based on distinct clinical features associated with anti-RNP antibodies, mixed connective tissue disease (MCTD) was described as a new autoimmune rheumatic disease in 1972 (6), although the disease entity of MCTD remains controversial in the rheumatological community. In Japan, the 2019 diagnostic criteria for MCTD developed by the Japan Research Committee of the Ministry of Health, Labor, and Welfare for systemic autoimmune diseases have been used widely (7). In the criteria, not only is the presence of anti-U1RNP antibody required, but so is at least one common manifestation, such as Raynaud's phenomenon, and at least one characteristic organ involvement, such as pulmonary arterial hypertension (Fig. 1) (7). Radin *et al*. (1) did not mention pulmonary hypertension by echocardiography and/or right heart catheterisation. UCTD has been defined as a condition characterised by the presence of symptoms and laboratory findings of CTD, but not fulfilling the existing classification criteria for any definite CTD (8). Thus, the patients diagnosed with anti-RNP antibody-positive UCTD in the study by Radin *et al*. (1) might have been diagnosed with MCTD from the beginning of follow-up under the Japanese diagnostic criteria for MCTD. An international validation study on new MCTD criteria is called for (7).

Table I. Evolution into definite CTD of UCTD patients with anti-Ro/SSA antibodies by ELISA.

Anti-Ro/SSA antibody positivity	No. of UCTD patients (total 131 patients)	No. of patients evolved into definite CTD (total 34 patients)	No. of patients with stable UCTD (total 97 patients)	p-value*
Both anti-Ro60- and anti-Ro52-antibody positive	77 (58.8%)	20 (58.8%)	57 (58.8%)	
Only anti-Ro60-antibody positive	6 (4.6%)	4 (11.8%)	2 (2.1%)	0.063
Only anti-Ro52-antibody positive	48 (36.6)	10 (29.4%)	38 (39.2%)	

*We added a statistical analysis by 3x2 Fisher's exact test on the previous study (4).
CTD: connective tissue disease; ELISA: enzyme-linked immunosorbent assay; No.: number; UCTD: undifferentiated connective tissue disease.

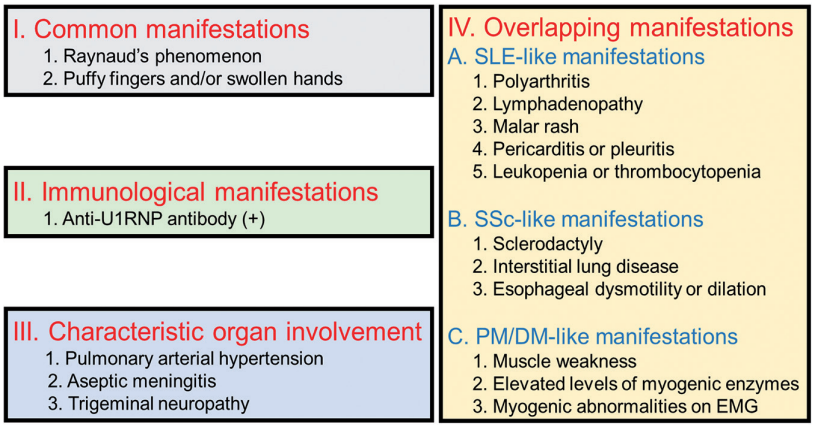

Fig. 1. Items in 2019 diagnostic criteria for mixed connective tissue disease from the Japan Research Committee of the Ministry of Health, Labor, and Welfare for systemic autoimmune diseases.
According to the criteria (7), mixed connective tissue disease is diagnosed in patients who fulfill either item i) or item ii): i) at least one common manifestation, immunological manifestation, and at least one characteristic organ involvement, ii) at least one common manifestation, immunological manifestation, and at least one feature each in 2 or more from items A, B, and C in overlapping manifestations.
DM: dermatomyositis; EMG: electromyogram; PM: polymyositis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis.

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