Decision-making value of nuclear dense fine speckled pattern in systemic autoimmune rheumatic disease: trick or treat?

We read with great interest the recommendation published by Damoiseaux *et al* and other members of the International Consensus on Antinuclear antibody (ANA) patterns (ICAP).[1] Not only the clinical relevance of human epithelial type 2 (HEp-2) indirect immunofluorescent (IIF) patterns was presented, suggestion about follow-up testing was also given in this article, which will benefit the clinical decision-making in daily practice. Nuclear dense fine speckled (DFS) pattern, a competent-level pattern evaluated by the ICAP previously (AC-02),[2] is frequently discussed in the current recommendation for it being the pattern best associated with apparently healthy individuals, or negatively correlating with systemic autoimmune rheumatic disease (SARD).

Damoiseaux *et al* demonstrated that the negative relationship between DFS pattern and SARD will be valid only if both specific DFS70 and other common extractable nuclear antigen (ENA) autoantibodies were not observed.[1] However, the testing strategies of DFS pattern remains controversy. Some proposed that the specific DFS70 autoantibodies should be detected after the screening DFS pattern by IIF, as suggested by Damoiseaux *et al*. Others process the ANA screening by immunoadsorption of anti-DFS70 before IIF or by a substrate that contains DFS70 knockout HEp-2 cells.[3] The discrepancy may originate from the unravel clinical decision-making value of DFS pattern. Hence, we reviewed our clinical data to aid in this discussion.

Results of routine diagnostic samples sent for a specific testing set of rheumatism (Jan until March 2019) were collected from Peking Union Medical College Hospital. The testing set contains ANA detected by IIF, and ENA autoantibodies detected by line immunoassay. Assays were performed according to the instructions (Euroimmune, Germany). Slides determining ANA were read by two experienced technologists. The patients with DFS pattern were diagnosed according to the related diagnostic criteria. Informed consent was waived due to the retrospective nature of the study.

A total of 5961 samples were sent for the testing set. The DFS pattern was observed in 58 patients (female to male ratio, 7.26) among the 2507 ANA-positive individuals. Twenty-one out of the 58 were diagnosed with autoimmune diseases, including 12 ANA-associated rheumatic diseases (two Sjögren's syndrome, two systemic lupus erythematosus, one myositis and seven connective tissue diseases), six antiphospholipid syndrome, one rheumatoid arthritis, one autoimmune hepatitis and one Behcet's disease. To be noted, ENA antibodies was not observed in one Sjögren's syndrome, one systemic lupus erythematosus and four connective tissue diseases. In other words, the DFS pattern is the only positive implication of autoimmune background for these six patients. Predictably, the diagnosis and treatment of them might be delayed if the immunoadsorption or knockout testing strategies of DFS pattern was applied to them. Though specific DFS70 autoantibodies was not detected, we estimated a 60% chance that these 12 patients would be excluded from the diagnosis of SARD according to the published prevalence of DFS70 autoantibodies in DFS pattern.[4]

Also, Damoiseaux *et al* demonstrated that the AC-02 of apparent health individuals or patients who do not have SARD may be produced by autoantigens other than DFS70.[1] Indeed, studies found that autoantigens MeCP2, c-MYC binding protein, and the mixed lineage leukaemia protein 1 could cause a DFS pattern,[5 6] while their clinical association with SARD has not been illustrated. Therefore, evaluating the clinical decision-making value of anti-DFS antibody should mainly base on the DFS pattern, which is also consistent with the widely accepted rule that screening ANA by IIF will provide more information than detecting the specific autoantibodies alone.[1 2]

A 4-year follow-up study found that none of the DFS-positive patients develop autoimmune diseases,[7] constituting a crucial evidence to establish the DFS as exclusion biomarker in SARD. It is well known that autoimmune disease is a chronic process, and some typical autoimmune markers can be detected as early as 10 years before the onset of disease, such as anticyclic citrulline polypeptide antibody in rheumatoid arthritis. Therefore, it will take longer period than 4 years to confirm the correlation between DFS and autoimmune disease.

In all, using sole positive of DFS70 antibody or DFS pattern as the exclusion criterion of SARD is attractive to a triage system of rheumatism, while this rule should be applied with caution referring to the results we reported. To demonstrate the significance of DFS pattern in SARD, longitudinal studies that applying both ANA screening by IIF and more novel antigen-specific immunoassays for DFS pattern are necessary.

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