Letters to the Editor

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Unifying abbreviations for biologics in rheumatology—does the idea hold promise?

Sir, Since presenting the idea of a unifying abbreviation system for biologics used in trials and in clinics some years ago [1], I have repeatedly been asked to both expand the list according to the three-letter system and to test whether all new substances can be coded without being ambiguous. The continuous development and licensing of additional biologics in all kinds of rheumatological disorders has helped significantly to achieve these goals, as has the persisting variety of abbreviations frequently observed even in the same satellite symposium addressing a given biological. In keeping with the original idea, in the updated list (Table 1) the added drugs are coded by the first two letters of the generic, e.g. IN for infliximab, ET for etanercept, AD for adalimumab, etc., and the third letter indicating the biological structure or class of the drug, i.e. X for a chimeric monoclonal antibody, Z for a humanized monoclonal antibody, M for a human monoclonal antibody, C for a soluble receptor/receptor–antibody fusion protein and R for a receptor antagonist.

Rheumatology key message

- This proposed coding system can be used for all current and future biologics.

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Table 1. Updated abbreviation list for currently used biologics in clinics, trials and publications in rheumatology and related medical specialities

Abbreviation/code	Biological/generic
ABC	Abatacept
ADM	Adalimumab
ALC	Alefacept
ALZ	Alemtuzumab
ANR	Anakinra
BAC	Baminercept
BAX	Basiliximab
BEM	Belimumab
BEZ	Bevacizumab
DEM	Denosumab
CAM	Canakinumab
CEZ	Certolizumab
DAZ	Daclizumab
ECZ	Eculizumab
EFZ	Efalizumab
EPZ	Epratuzumab
ETC	Etanercept
GOM	Golimumab
INX	Infliximab
NAZ	Natalizumab
OCZ	Ocrelizumab
OFM	Ofatumumab
ONC	Onercept
RIX	Rituximab
TAZ	Tanezumab
TOZ	Tocilizumab
USM	Ustekinumab

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Nailfold capillaroscopy abnormalities are associated with the presence of anti-endothelial cell antibodies in Sjogren's syndrome

Sir, Primary SS is often associated with vascular features such as RP, in 10–30% of the cases and vasculitis [1]. In SS microvascular abnormalities, assessed by nailfold capillaroscopy (NC), range from non-specific to more specific or scleroderma-type findings [2–4]. Patients with RP seem to have a higher frequency of NC abnormalities with respect to non-RP patients and a scleroderma-type NC pattern is associated with the presence of ACAs [2]. A higher deletion score on NC microscopy has been described in those SS patients with systemic manifestations and RP [3]. Avascularity has been recently confirmed to be associated with a reduction of the blood flow [4]. Until now no association has been described in SS between NC findings and serological parameters of endothelial damage, including anti-endothelial cell antibodies (AECAs), although these autoantibodies, claimed for a possible pathogenetic role in autoimmune diseases, have been detected in 25–30% of SS and seem to be more frequent in those patients presenting RP [5].

We investigated the microvascular involvement in a group of 66 consecutive primary SS patients, diagnosed according to the American–European Criteria [6] [65 females, 1 male; mean age 54.2 years (range 26–76 years); mean disease duration 108.8 months (range 6–372 months)], looking for any NC abnormalities and for AECAs. Patients gave their informed consent and underwent a careful clinical assessment. The study was approved by the local ethics committee.

Each patient performed NC, according to the standard method [7]. The following morphological parameters were considered: number of capillaries per square millimetre, alterations of the capillary length, morphology (tortuous, ramified/bushy capillaries) and distribution; presence of ectasic loops, haemorrhages and flux abnormalities [7]. A semi-quantitative rating scale was adopted to score these changes, according to previous studies [8]: score 0 = no changes; 1 = few = less than 4 alterations; 2 = some = between 4 and 6 alterations; 3 = frequent = more than 6 alterations per linear millimetre. The mean score for each subject was obtained analysing all fingers.

A full laboratory investigation included ESR, CRP, full blood count, ANA detection by indirect IF (Binding Site). Anti-SSA/Ro and anti-SSB/La antibodies were measured using an ELISA (DIAMEDIX, Miami, FL, USA). AECA serum levels were also measured. Briefly, human umbilical-vein endothelial cells were isolated by collagenase perfusion and were cultured in M199 medium (Sigma Chemical Co., St Louis, MO, USA).

These cells were used to detect AECA of IgG isotype by means of a cyto-ELISA as previously described [9]. Optical density (OD) was read at 405 nm wavelength and AECAs were expressed as a binding index (BI). AECAs were considered positive when the BI was higher than the cut-off value (mean + 2 S.D. of 66 healthy controls) corresponding to 50% of a positive reference serum from an SLE patient. Each serum sample was tested in duplicate.

The statistical analysis was performed analysing categorical variables by χ^2-test or Fisher's exact test and differences between the means were determined using Mann–Whitney test for unpaired samples. P-values < 0.05 were considered statistically significant. Twenty-six (39.4%) of the 66 SS patients presented RP, whereas an NC score $\geqslant 1$ was found in 33 cases (50%), ANAs were found in 55 patients (83.3%), anti-SSA/Ro antibodies in 47 (71.2%) and anti-SSB/La in 35 (53%) subjects. Sixteen (24.2%) patients had AECA. RP was present in 8 (50%) AECA-positive patients and in 17 (34%) patients without these autoantibodies. The presence of ANA inversely correlated with the presence of AECA in our patients (56 *vs* 92%) ($P < 0.003$). An NC score of $\geqslant 1$ was found in 13 (81.2%) AECA-positive patients (Fig. 1), with respect to 20 (40%) AECA-negative patients ($P < 0.008$). No association was found concerning the other clinical, capillaroscopic or laboratory features (Table 1).

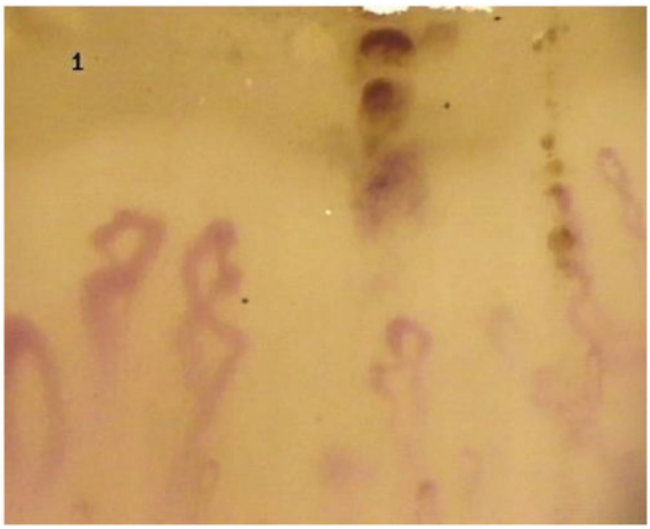

FIG. 1. NC of an SS patient with AECAs (score >1).

TABLE 1. Comparison of the main clinical–demographical and laboratory parameters in SS patients with and without AECA

	AECA+ patients ($n = 16$)	AECA− patients ($n = 50$)
M : F	1 : 15	0 : 50
Age, mean (range), years	52.5 (26–64)	56.5 (38–71)
Disease duration, mean (range), months	48 (11–372)	96 (6–360)
RP, *n* (%)	8 (50)	18 (36)
Xeropthalmia/xerostomia, *n* (%)	14 (87.5)	45 (90)
Articular involvement, *n* (%)	11 (68.8)	45 (90)
NC score $\geqslant 1$, *n* (%)*	13 (81.2)	20 (40)
Morphological abnormalities	11 (68.7)	35 (70)
Irregular distribution	6 (37.5)	9 (18)
Ectasic loops	9 (56.2)	16 (32)
Haemorrhages	4 (25)	16 (32)
Flux abnormalities	7 (43.7)	18 (36)
ANA+, *n* (%)**	9 (56)	46 (92)
Anti-SSA/Ro antibodies+, *n* (%)	11 (68.7)	36 (72)
Anti-SSB/La antibodies+, *n* (%)	7 (43.7)	28 (56)

*$P < 0.008$; **$P < 0.003$.

Even though a peculiar NC pattern has not been characterized to date in SS patients (2–4), our findings show that an NC score $\geqslant 1$ is detectable in 50% of the cases and is more frequent in AECA-positive patients with respect to those without these autoantibodies ($P < 0.008$). Although not significant, this group of patients also had a more frequent RP with respect to those without AECAs (50 *vs* 34%), as shown in previous studies, meaning that they may act with a mediated mechanism resulting in an increased vascular reactivity [5]. They also seemed to lack ANA with respect to AECA-negative patients, thus confirming a non-specific B-cell polyclonal activation in SS, where different antigenic targets may differently stimulate the autoantibody production. The detection of AECAs seems to be independent of the presence of antibodies with unrelated specificities, such as ANAs [10].

A high prevalence of AECAs has been frequently associated with the presence of vascular lesions and with disease activity in autoimmune diseases. However, it is difficult to define the role of SS in the occurrence of AECAs, whose endothelial antigenic targets are still unknown. The pathogenetic role of AECAs in the development of vascular injury remains controversial.

We know that NC is a useful tool for the assessment of microvascular involvement in many autoimmune diseases and it seems to be able to show early abnormalities [8]. The interesting association of these NC findings with the presence of AECAs suggests that these autoantibodies are involved in the determinism of the endothelial damage in SS. The contemporary presence of AECAs and more frequent NC abnormalities led us to sustain the hypothesis that these two parameters may help in evaluating the expression of vasculopathy in SS.

Rheumatology key message

- A more severe NC score is significantly associated with the presence of AECAs in SS.

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Cardiac infiltration in early-onset sarcoidosis associated with a novel heterozygous mutation, G481D, in *CARD15*

Sir, Early-onset sarcoidosis (EOS) and Blau syndrome (BS) are rare multi-organ granulomatous inflammatory disorders clinically characterized by the distinct triad of skin, joint and eye lesions without any apparent cardio-pulmonary involvement [1]. Gain-of-function mutations in *CARD15* (NM_022162) cause EOS and/or BS (EOS/BS) [2–4], but not the development of adult-type sarcoidosis [5, 6]. We identified a novel heterozygous gain-of-function mutation, G481D, in *CARD15* from a patient with EOS, who was suffering from recurrent episodes of congestive heart failure. Cardiac infiltration is a common clinical manifestation in adult-type sarcoidosis, but is rare and atypical in EOS/BS. Notably, the cardiac manifestations of this patient are quite similar to those in adult sarcoidosis. This is the first report demonstrating the precise manifestations of cardiac infiltration of sarcoidosis in a patient with a *CARD15* mutation.

The patient was an 18-year-old female. At 3 months of age she developed a miliaria-like skin rash. Thereafter, she presented various manifestations, such as uveitis, joint involvement, hepatosplenomegaly, arterial hypertension and congestive heart failure. A lymph node biopsy showed fresh-looking multiple granulomas, indicating a diagnosis of EOS. The administration of glucocorticoids improved her symptoms. However, extended treatments were required because of recurrent episodes of congestive heart failure accompanied with the activation of an autoinflammatory reaction. Echocardiography showed intraventricular septum thickness [Fig. 1A (a, b)]. A histopathological examination of the right ventricle endocardium revealed inflammatory cell infiltration, ballooning of myocardium and mild fibrosis (Fig. 1B). The histopathological findings were similar to those of cardiac sarcoidosis in adults. Other immunosuppressive treatments, e.g. NSAIDs, MTX, AZA and/or CSA, did not sufficiently improve her symptoms. The administration of TNF-α inhibitor, infliximab, in combination with MTX effectively inhibited the autoinflammation, thus resulting in an improvement of the intraventricular septum thickness [Fig. 1A (c, d)].

Under approval by the Ethics Committee/Internal Review Board of Hiroshima University and informed patient consent, we analysed the nucleotide sequence of *CARD15*, and found a novel heterozygous single base-pair substitution, 1442G>A (G481D), in exon 4. This mutation was located within the nucleotide-binding domain. NF-κB reporter assay revealed that MDP-independent NF-κB transactivation in the G481D, C495Y and H496L mutants in *CARD15* showed significantly higher levels than that in wild-type (WT) (Fig. 1C), thus suggesting the G481D mutation to be a gain-of-function mutation [3].

Cardiac infiltration is a rare and atypical manifestation among the patients with EOS/BS. Only one report has shown cardiac infiltration among the patients with *CARD15* mutations [4]. The patient suffered from severe multi-organ involvement, arterial hypertension and myocardial hypertrophy, and was identified as being a heterozygous C495Y mutation. The C495Y mutation displayed the highest level of MDP-independent NF-κB activation (Fig. 1C), and notably the G481D mutation also demonstrated a relatively higher level of activity. Although no genotype–phenotype correlation in EOS/BS could be proven in the previous study, cardiac infiltration may therefore be associated with higher levels of MDP-independent NF-κB activation [3].

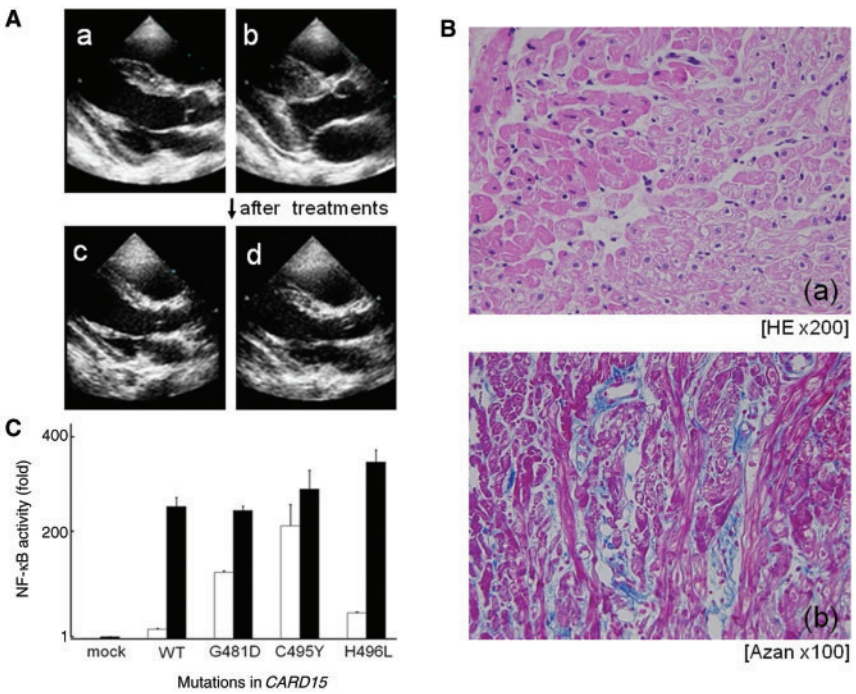

Fig. 1. (**A**) Echocardiography findings (parasternal long-axis view) before (a, b) and after (c, d) sufficient anti-inflammatory treatments. The systolic (a, c) and diastolic (b, d) image. (**B**) Histopathological findings of endocardium [(a) HE ×200, (b) Azan ×100]. (**C**) The MDP-independent (open columns) and MDP-dependent (filled columns) NF-κB transactivation. Values represent the mean of the normalized data (mock without MDP = 1) of triplicate cultures, and error bars indicate the S.D. Both C495Y and H496L are previously reported mutations in patients with EOS [3, 4].