Anti Ku antibody is associated with haematological manifestations but not with overlap features in systemic lupus erythematosus

Sirs,

Ku is a DNA-binding protein that has a substantial role in the repair of dsDNA breaks (1). The clinical implications of anti Ku antibodies in systemic sclerosis and inflammatory myositis are described in literature. In most studies they are associated with overlap features, such as parenchymal lung involvement, muscle weakness, arthritis and Raynaud's phenomenon (RP) (2-4). Spielmann *et al*. analysed anti Ku syndrome as a separate entity. In their cluster analysis with anti Ku syndrome patients, the cluster with a positive anti dsDNA, malar rash and cytopenia had more renal involvement (5). It seems that this cluster is formed mostly by patients with systemic lupus erythematosus (SLE). Hence, we tried to assess the clinical characteristics of SLE patients with anti Ku positivity through a retrospective case control analysis.

Anti Ku antibody is detected by line immunoassay (Euroimmune, Germany) in our laboratory. The line immunoassay registry of SLE patients satisfying SLICC criteria was searched for anti Ku positive patients and their medical records were retrieved. Clinical details at the time of presentation were extracted using a pre-specified proforma. The clinical features were defined as in SLICC criteria (6). Anti Ku negative controls were generated from the same registry using a computer-generated random number in a ratio 1:2. The statistical analysis was done using SPSS v. 19. Quantitative data were analysed using Student's t-test or Mann-Whitney U-test and proportions were tested using Chi-square or Fisher's exact test as appropriate. Binary logistic regression was used to further characterise patients. The study was approved by the institute ethics committee and conducted following Principles of declaration of Helsinki (1964) and its later amendments or comparable ethical standards.

Out of the 1155 SLE patients screened, 89 (7.7%) had anti Ku positivity and medical records were available for 79. One hundred and fifty-eight controls who were negative for anti Ku were selected from the same registry. The mean age of anti Ku positive patients was 26.6±10.5yrs with a female/male ratio of 19:1 (Table I). Illness duration was shorter in anti Ku positive patients. On univariate analysis, haematological manifestations (autoimmune haemolysis, leucopenia and thrombocytopenia taken together) were more common in anti Ku positive patients and arthritis was less prevalent. They also had higher prevalence of anti dsDNA antibody positivity and low levels of serum complement 3 (C3). On binary logistic regression, only duration of illness was significantly different. Anti Ku positive patients with a positive anti dsDNA antibody had more renal involvement (64% *vs*. 32%, OR 3.7, 1.4–9.8, p=0.005) but persay anti Ku alone was not associated with renal manifestations. But the higher prevalence of haematological manifestations was independent of anti dsDNA positivity. Prevalence of overlap features like muscle weakness, RP, ocular and oral sicca and pulmonary artery hypertension were comparable among the groups. Two patients with interstitial lung disease (ILD) were anti Ku negative.

In our cohort, those with anti Ku antibody positivity had shorter duration of illness with a higher prevalence of haematological manifestations. Presence of anti dsDNA antibodies in them increased the risk of renal involvement. The third cluster of Spielmann *et al*. had similar clinical features (5). Being a dsDNA repair protein, anti Ku antibodies may have a role in production of anti dsDNA antibodies, or it may be due to epitope spreading. Unlike previous studies in non SLE anti Ku syndromes, the prevalence of overlap features was not different (2-4). Moreover, arthritis was less common and ILD was not seen. This suggests that anti Ku antibodies may be behaving differently in different disease settings. The retrospective design is a limitation of the study. In conclusion, anti Ku antibody is associated with haematological involvement in SLE and the study substantiates the findings of a cluster of "anti-Ku with anti-dsDNA" among anti Ku syndrome

Table I. Characteristics of SLE patients at the time of presentation.

Variable/group	Total (n=237)	AntiKu positive (n=79)	AntiKu negative (n=158)	OR with 95% CI	p
Mean age in yrs(±SD)	27.8±9.7	26.6±10.5	28.4±9.2		0.19
Male:Female	1:19	1:19	1:19		1.0
Juvenile onset* (%)	35 (14.8)	16 (20.2)	19 (12.0)	0.09	
Duration of illness (IQR)	12 (4,24)	6 (4,24)	12 (5,36)	**0.006**	
Constitutional (%)	168 (70.9)	57 (72.2)	111 (70.3)	1.09 (0.60 to 1.99)	0.76
ACLE (%)	106 (44.7)	41 (51.9)	65 (41.1)	1.54 (0.89 to 2.65)	0.12
CCLE (%)	58 (24.5)	21 (26.6)	37 (23.4)	1.18 (0.63 to 2.20)	0.59
Haematological** (%)	98 (41.4)	47 (59.5)	51 (32.2)	3.08 (1.76 to 5.39)	**0.001**
Leucopenia (%)	58 (24.5)	28 (35.4)	30 (18.9)	2.34 (1.27 to 4.31)	**0.005**
Thrombocytopenia (%)	30 (12.7)	13 (16.5)	17 (10.8)	1.63 (0.75 to 3.56)	0.21
AIHA (%)	42 (17.7)	22 (27.8)	20 (12.7)	2.74 (1.39 to 5.42)	**0.003**
Arthritis (%)	124 (52.3)	34 (43)	90 (57)	0.57 (0.33 to 0.99)	**0.04**
Renal involvement (%)	96 (40.5)	36 (45.6)	60 (38.2)	1.42 (0.82 to 2.46)	0.21
NPSLE (%)	23 (9.7)	8 (10.1)	15 (9.5)	1.07 (0.44 to 2.65)	0.87
Any cardiac involvement (%)	62/186 (33.3)	18/55 (32.7)	44/131 (33.5)	0.96 (0.49 to 1.88)	0.91
Muscle weakness (%)	25/185 (13.5)	7/55 (12.7)	18/130 (13.8)	0.91 (0.36 to 2.31)	0.83
PAH (%)	22/180 (12.2)	7/53 (13.2)	15/127 (11.8)	1.14 (0.44 to 2.97)	0.79
Raynaud's phenomenon (%)	14/183 (7.7)	2/53 (3.8)	12/130 (9.2)	0.39 (0.08 to 1.79)	0.2
Oral/ocular sicca (%)	14/185 (7.6)	3/55 (5.5)	11/130 (8.5)	0.62 (0.16 to 2.33)	0.48
Anti dsDNA positive (%)	129 (54.4)	35 (44.3)	46 (29.1)	1.94 (1.11 to 3.39)	**0.02**
Low C3 (%)	165/211 (78.6)	58/66 (87.9)	107/145 (73.8)	2.58 (1.13 to 5.89)	**0.02**
Low C4 (%)	117/211 (55.4)	42/66 (63.6)	75/145 (51.7)	1.63 (0.89 to 2.97)	0.10

*age of onset below 16 years; **AIHA: leucopenia and thrombocytopenia taken together; ACLE: acute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; AIHA: autoimmune haemolytic anemia; PAH: pulmonary artery hypertension; NPSLE: neuropsychiatric SLE.

patients who have predominant renal involvement, which is more likely due to dsDNA *per se* than anti KU antibody.

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