ASSOCIATION OF ANTI-KU AUTOANTIBODIES AND SOME ORGAN DAMAGE OF AUTOIMMUNE CONNECTIVE TISSUE DISEASES

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ABSTRACT

Objectives: To assess the association between anti-Ku antibodies and organ damage in common autoimmune connective tissue diseases.

Materials and method: This was a descriptive, cross-sectional, retrospective, and prospective study involving 215 patients diagnosed with autoimmune connective tissue diseases, including systemic sclerosis, systemic lupus erythematosus, dermatomyositis, and overlap syndromes of ACTDs, treated at the National Hospital of Dermatology and Venereology from January 2021 to December 2022. Patients were tested for the presence of anti-Ku antibodies using the ANA 23 profile test kit.

Results: Out of the 215 patients in the study, 60 (27.9%) tested positive for anti-Ku antibodies, predominantly at a weak level (1+). Among these, 43.3% had systemic lupus erythematosus, 10% had systemic sclerosis, 18.3% had dermatomyositis, and 28.3% had overlap syndromes of ACTDs. The group with positive anti-Ku antibodies exhibited a higher incidence of butterfly rash and mouth ulcers. The positive anti-Ku antibody group had a significantly higher rate of elevated muscle enzymes (53.3%) compared to the negative group (29.7%) ($p = 0.001$). Additionally, the incidence of pulmonary arterial hypertension was 39.5%, with the positive anti-Ku antibody group having a higher rate (61.7%) than the negative group (31%) ($p < 0.05$). High-resolution computed tomography revealed interstitial lung lesions in 37.2% of the patients, with no significant difference between the positive and negative groups.

Conclusions: Anti-Ku antibodies are relatively prevalent in patients with autoimmune connective tissue diseases, particularly in systemic lupus erythematosus and overlap syndromes of ACTDs. Patients with positive anti-Ku antibodies are at a higher risk of developing acute skin lesions in systemic lupus erythematosus, muscle damage with elevated muscle enzymes, and pulmonary arterial hypertension compared to those without these antibodies.

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1. INTRODUCTION

Autoimmune connective tissue diseases (ACTDs) represent a group of autoimmune disorders characterized by abnormalities in connective tissue, chronic progression, and unclear pathogenesis. These diseases can cause damage to the entire connective tissue, presenting with diverse clinical manifestations across multiple organs, including the skin, lungs, and kidneys, to varying degrees[1]. There are several types of autoimmune connective tissue diseases, with the four most common being systemic sclerosis, systemic lupus erythematosus, dermatomyositis, and the overlap syndrome of autoimmune connective tissue diseases[1,2].

Research into autoimmune connective tissue diseases has shown the presence of various accompanying autoantibodies, which are associated with both clinical manifestations and pathophysiological mechanisms. Many of these autoantibodies serve as specific markers for diagnosing autoimmune connective tissue diseases and play a role in predicting organ damage[3]. Among these, anti-Ku antibodies (which target the Ku protein, a highly immunogenic protein involved in DNA repair) can be found in autoimmune connective tissue diseases at varying rates. These antibodies were first described in 1981 in patients with overlap syndromes of scleroderma and dermatomyositis[4]. Anti-Ku antibodies have been reported in several connective tissue diseases, including systemic lupus erythematosus, Sjögren's syndrome, idiopathic pulmonary fibrosis, and the overlap syndrome of scleroderma and myositis. Clinical symptoms observed in patients with anti-Ku antibodies primarily include myositis, arthritis, and Raynaud's phenomenon. In these cases, anti-Ku antibodies are often detected alongside other antibodies such as Ro and anti-nuclear antibodies[5,6].

In Vietnam, as well as globally, studies on anti-Ku antibodies and their clinical and laboratory characteristics in patients with autoimmune connective tissue diseases are limited and fragmented. Therefore, we conducted this study to evaluate the relationship between anti-Ku antibodies and organ damage in autoimmune connective tissue diseases.

2. SUBJECTS AND METHODS

2.1. Study subjects

The selection criteria included patients diagnosed with autoimmune connective tissue diseases, specifically systemic lupus erythematosus, systemic sclerosis, dermatomyositis, and overlap syndromes, who visited and received treatment at the National Hospital of Dermatology and Venereology from January 2021 to December 2022. Patients underwent testing for anti-Ku antibodies using the ANA 23 Profile test and additional assessments to evaluate organ damage. Exclusion criteria included patients who did not meet the selection criteria.

2.2. Study methods

Study design

This was a descriptive, cross-sectional study that combined retrospective and prospective elements. Retrospective data were collected from eligible patient records starting from January 2021. New patients were included from January 2022 to December 2022. Data collection continued until the end of the study period.

Procedures

For retrospective patients, administrative information, clinical examination findings, and

laboratory test results were gathered from patient records stored in the hospital's planning department and from records of other studies previously conducted at the National Hospital of Dermatology and Venereology.

Prospective patients had their medical records established using a designated study template. Subsequently, they underwent testing for anti-Ku antibodies with the ANA 23 Profile kit and additional assessments for organ damage, which included complete blood count, blood biochemistry, urinalysis, anti-nuclear antibody testing, echocardiography, chest X-ray, high-resolution computed tomography of the lungs, and pulmonary function tests. Data were compiled to calculate the prevalence of anti-Ku antibodies and organ damage in autoimmune connective tissue diseases.

Statistical analysis

Collected data were entered, managed, and analyzed using SPSS software version 20.0. Statistical comparisons for qualitative variables within the same group used the McNemar's test; comparisons between two groups used the Chi-square test, with Fisher's exact test applied if the expected value was less than 5. For quantitative variables, T-tests were used to compare means between two independent samples. Statistical significance was defined as $p < 0.05$.

2.3. Ethics

Personal information of patients was kept confidential and used solely for the purpose of this study, in accordance with the Helsinki 2013 guidelines. This study was approved by the National Hospital of Dermatology and Venereology and was reviewed by the hospital's ethics committee.

3. RESULTS

3.1. Anti-Ku antibodies in patients with autoimmune connective tissue diseases

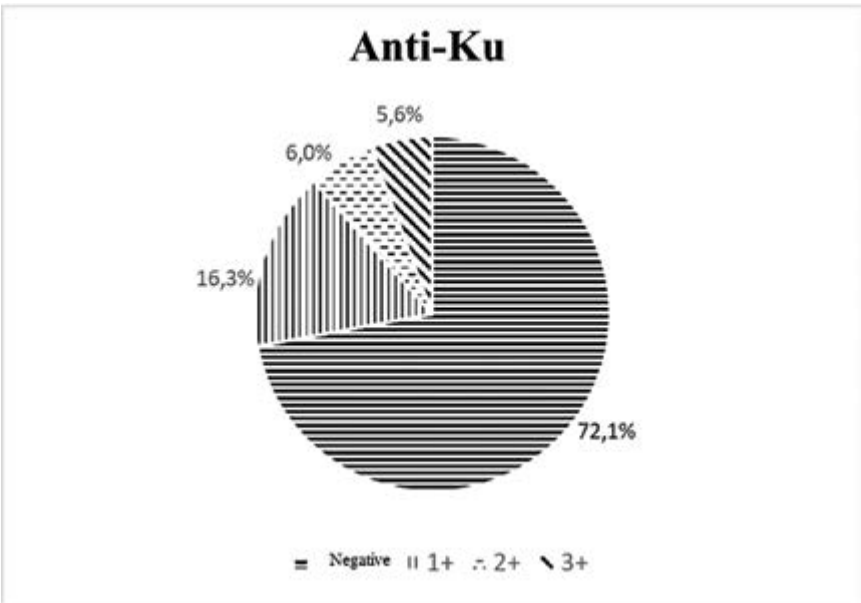

Figure 1. Prevalence of Anti-Ku antibodies in patients with autoimmune connective tissue diseases (N = 215)

There were 60 patients with positive anti-Ku antibodies out of a total of 215 patients (38 cases were retrospective, accounting for 17.7%) with autoimmune connective tissue diseases participating in the study. This group included 58 patients with systemic sclerosis, 60 patients with systemic lupus erythematosus, 40 patients with dermatomyositis, and 57 patients with overlap syndrome, representing a total positivity rate of 27.9%. Among these, the majority of positive anti-Ku antibodies were at a level of 1+, which was the highest proportion.

3.2. Anti-Ku Antibodies in Autoimmune Connective Tissue Diseases

Table 1. Prevalence of Anti-Ku antibodies in autoimmune connective tissue diseases (N = 215)

No.	Disease	Positive (n)	Percentage (%)
1	Systemic Sclerosis (n = 58)	6	10.3
2	Systemic Lupus Erythematosus (n = 60)	26	43.3
3	Dermatomyositis (n = 40)	11	27.5
4	Overlap Syndrome (n = 57)	17	29.8
5	Total (N = 215)	60	27.9

Out of 215 patients studied, 60 were found to be positive for anti-Ku antibodies, yielding a positivity rate of 27.9%. Among these, the highest positivity was found in the systemic lupus erythematosus group (43.3%), followed by the overlap syndrome group (29.8%), the dermatomyositis group (27.5%), and the systemic sclerosis group (10.3%).

3.3. Clinical Characteristics of patients with positive Anti-Ku antibodies

Table 2. Anti-Ku antibodies and skin manifestations (N = 215)

Type of Lesion		Anti-Ku		p*
		Positive	Negative	
Butterfly rash	Present	22 (36.7%)	34 (21.9%)	**0.027**
	Absent	38 (63.3%)	121 (78.1%)	
Oral ulcer	Present	15 (25%)	19 (12.3%)	**0.022**
	Absent	45 (75%)	136 (87.7%)	
Finger edema	Present	8 (13.3%)	23 (14.8%)	0.778
	Absent	52 (86.7%)	132 (85.2%)	
Sclerodactyly	Present	17 (28.3%)	72 (46.5%)	**0.016**
	Absent	43 (71.7%)	83 (53.6%)	

Type of Lesion		Anti-Ku		p*
		Positive	Negative	
Poikiloderma	Present	6 (10%)	31 (20%)	0.081
	Absent	54 (90%)	124 (80%)	
Heliotrope sign	Present	7 (11.7%)	28 (18,1%)	0.254
	Absent	53 (88.3%)	127 (81,9%)	
Gottron's sign	Present	13 (21.7%)	33 (21,3%)	0.952
	Absent	47 (78.3%)	122 (78,7%)	
Gottron's papules	Present	8 (13.3%)	17 (11%)	0.627
	Absent	52 (86.7%)	138 (89%)	

**Chi-square test.*

The prevalence of butterfly rash and oral ulcers was higher in the anti-Ku positive group compared to the negative group, with statistically significant differences ($p < 0.05$). Conversely, the prevalence of sclerodactyly was lower in the anti-Ku positive group.

3.4. Anti-Ku antibodies and muscle damage

Table 3. Anti-Ku antibodies and muscle damage (N = 215)

Type of Lesion		Anti-Ku		p*
		Positive	Negative	
Muscle pain	Present	10 (23.3%)	21 (13.6%)	0.121
	Absent	33 (76.7%)	134 (86.5%)	
Muscle weakness	Present	6 (14%)	14 (9%)	0.343
	Absent	37 (86.1%)	141 (91%)	
Elevated CK (CK > 190)	Present	32 (53.3%)	46 (29.7%)	**0.001**
	Absent	28 (46.7%)	109 (70.3%)	

**Chi-square test.*

The prevalence of elevated CK levels was significantly higher in the anti-Ku positive group ($p < 0.05$), while muscle pain and weakness showed no significant differences between the two groups.

3.5. Anti-Ku antibodies and peripheral vascular damage

Table 4. Anti-Ku antibodies and peripheral vascular damage (N = 215)

Type of Lesion		Anti-Ku		p*
		Positive	Negative	
Raynaud's phenomenon	Present	24 (40%)	85 (54.8%)	**0.049**
	Absent	36 (60%)	70 (45.2%)	

Type of Lesion		Anti-Ku		p*
		Positive	Negative	
Scarring at fingertips	Present	10 (16.7%)	35 (22.6%)	0.339
	Absent	50 (83.3%)	120 (77.4%)	
Fingertip ulcers	Present	0 (0%)	13 (8.4%)	0.21
	Absent	60 (100%)	142 (91.6%)	
Fingertip necrosis	Present	1 (1.7%)	1 (0.7%)	0.484
	Absent	59 (98.3%)	154 (99.4%)	
Nailfold capillary dilation	Present	18 (30%)	81 (52.3%)	**0.003**
	Absent	42 (70%)	74 (47.7%)	
Periungual Hemorrhage	Present	0 (0%)	5 (3.2%)	0.159
	Absent	60 (100%)	150 (96.8%)	

**Chi-square test.*

The prevalence of Raynaud's phenomenon was lower in the anti-Ku positive group, whereas nailfold capillary dilation was significantly higher ($p < 0.05$).

3.6. Anti-Ku antibodies and lung damage

Table 5. Anti-Ku antibodies and lung damage (N = 215)

Type of Lesion		Anti-Ku		p*
		Positive	Negative	
Pulmonary fibrosis on X-ray	Present	7 (16.3%)	29 (18.7%)	0.715
	Absent	36 (83.7%)	126 (81.3%)	
Pulmonary fibrosis on CT	Present	17 (28.3%)	63 (40.7%)	0.094
	Absent	43 (71.7%)	92 (59.4%)	
Pulmonary arterial hypertension	Present	37 (61.7%)	48 (31%)	**0.000**
	Absent	23 (38.3%)	107 (69%)	

**Chi-square test.*

The prevalence of pulmonary fibrosis detected via CT scans was higher than that detected on X-rays. Additionally, the rate of pulmonary arterial hypertension was significantly higher in the anti-Ku positive group ($p < 0.05$).

4. DISCUSSION

Anti-Ku antibodies are found in mixed connective tissue disease, but they also appear in many other autoimmune disorders. In our study involving 215 patients, 60 tested positive for anti-Ku antibodies, accounting for 27.9%. The highest positivity was at level 1+ (16.3%), followed by 2+ (6.0%) and the lowest at 3+ (5.6%). Among these, patients with systemic lupus erythematosus (SLE) had the highest positivity rate at 43.3%, followed by those with overlap syndrome (29.8%), dermatomyositis (27.5%), and systemic sclerosis, which had the lowest at 10.3%.

These results are higher than previous studies on the prevalence of anti-Ku antibodies, such as M. Yaneva et al., who reported only 19% in systemic lupus erythematosus and 14% in systemic sclerosis patients[7]. A study by Cavazzana et al. found that anti-Ku antibodies were positive in 2% of systemic sclerosis patients and 1.8% in lupus patients[8]. The differences in study populations, racial groups, and methods of detecting anti-Ku antibodies (such as immunoblot, immunoprecipitation, or ELISA) are key factors contributing to the variation in prevalence among studies.

The rate of butterfly rash and oral ulcers was higher in the anti-Ku positive group compared to the negative group, with statistically significant differences ($p < 0.05$). This indicates that characteristic acute skin lesions in patients with systemic lupus erythematosus are more prevalent among those with anti-Ku antibodies. The incidence of sclerodactyly was lower in the anti-Ku positive group compared to the negative group (28.3% vs. 71.7%). In the dermatomyositis group, there were no significant differences in skin lesions between the two groups.

There are few studies on the correlation between anti-Ku antibodies and skin lesions worldwide, and our research is one of the first conducted in Vietnam. We found that in patients with systemic lupus erythematosus and systemic sclerosis, specific skin lesions are associated with the presence of anti-Ku antibodies. However, to further validate these results, additional studies with larger sample sizes over longer periods are needed.

Muscle damage in autoimmune connective tissue diseases is clinically manifested by symptoms of muscle pain and weakness; however, many patients exhibit subclinical muscle damage indicated by elevated CK levels (CK > 190 U/l). In our study, the rate of clinical manifestations such as muscle pain was 14.4%, weakness 9.3%, with no significant differences between the anti-Ku positive and negative groups. Conversely, the incidence of elevated CK levels was significantly higher in the anti-Ku positive group (53.3% vs. 29.7%, $p = 0.005$). These results are consistent with previous studies regarding the relationship between anti-Ku antibodies and muscle damage. Cavazzana et al. reported that muscle inflammation and elevated CK levels occurred in 30% of patients with anti-Ku positivity.[7] Other studies indicate that anti-Ku antibodies are commonly found in patients with dermatomyositis/polymyositis and overlap syndromes among other autoimmune connective tissue diseases[6,8].

Peripheral vascular damage can occur early in autoimmune connective tissue diseases, commonly presenting as Raynaud's phenomenon and capillary changes. In some cases, late-stage manifestations can lead to nail bed hemorrhages and severe complications such as ulcers, scarring, and digital necrosis. The results in Table 3.4 indicate that the incidence of Raynaud's phenomenon and capillary dilation was higher in the anti-Ku negative group compared to the positive group (54.8% vs. 40% and 52.3% vs. 30%). This contrasts with earlier studies by Cavazzana et al. and Hoa et al.,[8,9] where the incidence of Raynaud's phenomenon was found to be 66.7% in patients with positive anti-Ku antibodies and capillary dilation was significantly higher (70%) with no differences noted between the anti-Ku positive and negative groups.

For nail bed scarring, ulcers, necrosis, and nail hemorrhage, there were no statistically significant differences between the two groups.

Thus, the results indicate that anti-Ku antibodies do not correlate with late-stage peripheral vascular damage in the study population. These discrepancies may be attributed to racial factors and differences among patient groups in autoimmune connective tissue diseases. Additionally, our study's sample size may not be sufficient, indicating the need for further research with longer follow-up periods.

Interstitial lung disease and pulmonary hypertension are two significant conditions that greatly impact the treatment and prognosis of autoimmune connective tissue diseases. In our study, the rate of interstitial lung disease detected by chest X-ray was 16.7%, lower than the rate detected by high-resolution computed tomography (HRCT), which was 37.2%. The incidence of interstitial lung disease in the anti-Ku positive group showed no statistically significant differences compared to the negative group. This differs from Hoa et al., who found higher rates of interstitial lung disease in the anti-Ku positive group (58% vs. 34% in the negative group)[9]. This may be due to the fewer instances of lung disease in the early stages of systemic lupus erythematosus in our study compared to patients who typically present with early interstitial lung disease.

On the other hand, the rate of pulmonary hypertension detected by echocardiography (with estimated pulmonary artery pressure ≥ 35 mmHg) was higher in the anti-Ku positive group than in the negative group, with a statistically significant difference ($p < 0.05$). This is consistent with findings from Hoa et al[9]. Therefore, the presence of anti-Ku antibodies may predict the progression of pulmonary hypertension, one of the severe complications that significantly affect the quality of life and mortality rates among patients.

5. CONCLUSIONS

Anti-Ku antibodies are present in 27.9% of patients with common autoimmune connective tissue diseases, with the highest positivity in systemic lupus erythematosus patients. The most frequent positivity level is low 1+. There is a correlation between anti-Ku antibodies and acute skin lesions such as butterfly rash and oral ulcers in systemic lupus erythematosus patients, as well as elevated CK levels and pulmonary hypertension. Patients who test positive for anti-Ku antibodies have a higher incidence of muscle damage and pulmonary hypertension compared to those who test negative.

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