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Original Research Article

# Clinical and serological evaluation of anti-Ku antibody positive patients by using line immunoassay (LIA) platform in patients' attending a tertiary care hospital in Bihar

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***Abstract***

***Aim:*** *to evaluate the clinical presentations of patients with Ku antibody positivity depending on the grades of staining and evaluate the pattern of anti-Ku antibody positivity depending on intensity of bands observed.*

***Material and methods:*** *This was a retrospective study conducted in the Department of Biochemistry, AIIMS Patna, from April 2019 to January 2020, which are positive/ equivocal for anti-Ku-antibody. A total of approximately 120 samples positive or equivocal for anti-Ku antibody will be analysed further for clinical data. Venous blood is collected under aseptic conditions in vacutainers without anticoagulant and put to centrifugation for serum separation. The sample was processed by Line immunoassay (LIA)for detection of anti-nuclear antibody panel which includes antibodies to 17 antigens.*

***Results:*** *The 120-130 anti-Ku positive sera were studied.50 of them were affected by systemic autoimmune diseases, whereas we did not have any clinical notice of threesubjects.All 50 anti-Ku positive patients were affected by systemic autoimmune diseases, mainly represented by UCTD in nine cases (32%) and overlap syndromes in eight cases(26%),including PM or Dermatomyositis (DM)/SScin 9 cases and PM/SLE in 2 case. Additional 9 subjects showed a diagnosis of SLE, 6 were affected by primary SS, 4 by PM whereasSScandRAweredetectedin2patientseach. Considering the total systemic autoimmune diseases followed by our Centre, anti-Ku antibodies are detected in 12 SSc patients (11 in overlap with PM/DM and one isolated) out of 120 total SSc cases (10%) and in 11 SLE (9 isolated and 2 case in overlap with PM) out of 120 total SLE cases (9.17%). In addition, they were found in nine UCTD patients out of 120(13.33%) and more rarely in primary SS and RA. Articular symptoms (subjective arthralgiasand poly- arthritis) and Raynaud's phenomenon represents the main clinical features observed in our series, detected in 80%, 48% and 64% of patients respectively. In addition, xerostomia and xerophtalmia were reported in 62% and 19 patients 38%, and about 28% of subjects showed myositis.Pulmonary interstitial disease was detected in 20 cases (40%) with a severe and progressive reduction of DLCOin20 patients(40%)and neutrophilicalveolitisin ten. Pulmonary hypertension was recorded in 5 cases. Most of patients with pulmonary involvement showed a diagnosis of PM ,SSc or PM/SSc overlap syndrome(11cases),where as the others were affected by UCTD (six cases), RA and primary SS (one case, each). Anti-Ku were detected in 36 sera as single anti-ENAspecificity(72%),whilenineserashowedmultiple anti-ENA antibodies, namely anti-Ku with anti- Ro/SSA (globally in 13 cases), with anti-La/SSB (4 cases), with anti-Ki antibodies (globally in 3 cases). In addition, anti-dsDNA antibodies were detected in 16 sera (32%), whereas anti-cardiolipinand anti-β2GPI antibodies were found in 26% and 22% of casesrespectively.*

***Conclusion:*** *We conclude that the anti-Ku antibodies are found in different systemic autoimmune diseases and frequently associated with myositis and interstitial pulmonary involvement. Anti-Ku antibodies are usually detected in association with other serological markers in SLE and pSS, while they could occur isolated in SSc and PM.*

## I. INTRODUCTION

Autoimmune disorders are a condition in which self immune system mistakenly targets the body′s own cells and tissue. The immune system normally protects our body against harmful substances like bacteria, viruses, toxins and cancer cells. The exact cause of autoimmune disorders is unknown .One theory is that some organism or drugs may trigger changes that leads to immune system confused between self and non-self tissue or cells.Approximately more than 80 autoimmune disorders have been discovered.[1]The diagnosis of autoimmune diseases depends on presence of autoantibody in the serum as well as clinical features. Antinuclear antibodies (ANA) have been recognised as diagnostic markers for groups of autoimmune diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis, mixed connective tissue disorder, systemic sclerosis etc. ANA are directed against self-cell nuclear and cytoplasmic components. ANA antibody is the hallmark of autoimmune disease but it can also be found in chronic disease and cancer patients.

ANA are also seen in normal individuals but its titres are high in patients of autoimmune disorder, thus serving as a marker for the diagnosis and prognosis.[2]ANA detected by the many methods but traditionally it is measured by the Line Immunoassay (LIA) and Indirect Immunofluorescence (IIF).By the use of LIA only 17 types of extractable autoantibodies like SmD1, PCNA , Nucleosomes, Ku, Mi-2,SS-A/RO60,JO-1,PM-SCl, CENP-B, SS-B/La, histones, SS-A/RO52, dsDNA,U1-SnRNP, AMA-M2, SCl- 70and P0 can be detected.

Antibodies to Ku antigen is originally found in patients with scleroderma-polymyositis overlap syndrome. Reports have shown that anti-Ku antibodies are also found in various diseases, mainly in patients with Systemic Lupus Erythematosus,systemic sclerosis and undifferentiated connective tissue diseases (UCTD).[3]

Anti-Ku antibodies, initially described in 1981 by Mimori et al. in scleroderma patients[4], have been further reported in a large groups of systemic autoimmune disease.[5,6] The Ku protein is a heterodimer made up of P70 and P80 subunits, that play fundamental role in DNA repair of double stranded DNA breaks through the non –homologous end joining (NHEJ) pathway.[7,8] Along with DNA repair Ku complex plays major role in replication, regulation of transcription, telomere maintenance, V (D) J recombination and development of brain.Ku is ubiquitously found in the nucleus, as well as it has also been found in the cytoplasm and on the cell surface.[9,10,11] In humans KuP70and KuP80 genes located on different chromosomes 22q13 and 2q33 respectively.

Anti-Ku reactivity was investigated with different methodological approaches in different studies. While Mimori, *et al* originally used immunodiffusion assay to detect anti-Ku antibodies, other investigators have used ELISA, immunoblot (IB), or immunoprecipitation assays.[12,13,14] Currently, the prevalence of antibodies to Ku protein in various autoimmune diseases varies widely ranging from 3% with IB analysis to 55% using a capture ELISA.[15]

The clinical symptoms described in patients presenting with anti-Ku-antibodies are mainly muscular weakness, myalgia, arthritis, oral ulcer, dysphagia, exertional dysnea, and Raynaud's phenomenon .Furthermore, recent data report that transient cranial neuropathy involving trigeminal and facial nerves could be another symptom of an autoimmune disease associated with anti-Ku antibodies.[16]

## II. MATERIAL AND METHODS:

This was a retrospective study conducted in the department of Biochemistryfrom April 2019 to January 2020(11 months), which are positive/ equivocal for anti-Ku-antibody. A total of approximately 120 samples positive or equivocal for anti-Ku antibody will be analysed further for clinical data.Patient’s result data was categorised age and sex wise. The present study was conducted in the department of Biochemistry, AIIMS Patna. . This research has approved by institutional ethical committee of AIIMS, Patna, Bihar. This study was extract the data from the samples tested using the following protocol.

**Inclusion criteria**

All samples received in Biochemistry central lab for ANA profile.

**Exclusion criteria**

All lipemic, icteric and haemolysed sample excluded (repeat sample accepted).

Methodology

Venous blood is collected under aseptic conditions in vacutainers without anticoagulant and put to centrifugation for serum separation. The separated serum is stored in -20 degree refrigerator in mini centrifuge vials till analysis.Clinical data was collected for previously admitted patients through medical records available in MRD after due permission of competent authority and through HIS.

The sample was processed by Line immunoassay (LIA)for detection of anti-nuclear antibody panel which includes antibodies to 17 antigens(dsDNA,nucleosome,histone,SmD1, PCNA, P0,SS-A/Ro52,SS-A/Ro60,SS-B/La, CENP-B, Scl-70,U1-snRNP,AMA-M2,Jo-1,PM-Scl,Mi-2 and Ku).LIA is an indirect membrane based enzyme immunoassay for the qualitative measurement of IgG class antibodies against the above mentioned seventeen nuclear antigens in human serum or plasma. The kits used provided by Human Diagnostics (IMTEC-ANA-LIA MAXX) and the instrument used is semi-automated analyser OZOBLOT 40M provided by Medsource Ozone Biomedicals.

**Principle of the test:**

The test is based on the principle of line immunoassay.Nuclear and associated cytosolic antigens are applied as lines on a nitrocellulose membrane .The nitrocellulose membrane are blocked to prevent unspecific reactions.During incubation of a strip with diluted patient's samples auto-antibodies present in the sample will bind to the antigens on the strip .For the detection of the bound antibodies a secondary horse radish peroxidase (HRP)-labelled anti-human IgG antibody is used. After addition of the substrate and stop solution the appearance of brown lines indicate the presence of (auto) antibodies against the respective antigens.

The interpretation of the test results takes place exclusively on the basis of the respective cut-off control regarded for each strip

**Statistical analysis:**

Data entered in Microsoft excel and analysed using SPSS version12.The association between qualitative variables were analysed using Chi-square test and that between quantitative variables was calculated using t-test. The p-value of <0.5 will be significant. Cluster analysis was performed the K –means algorithm to group patients having similar autoantibody profiles together. However, K- means clustering is intended for clustering quantitative variables, and the presence of autoantibody production is categorical. Factor analysis therefore is performed first with factor loading scores used in the k – means algorithm.

## III. RESULTS

In our study 56% and 44% female were participated most of the patients was 30-40 years followed by 20-30 years.

**Table 1 Demographic Profile of Patients**

| **Gender** | **N=50** | **%** |
|---|---|---|
| Male | 28 | 56 |
| Female | 22 | 44 |
| **Age (years)** | | |
| Below 20 | 8 | 16 |
| 20-30 | 12 | 24 |
| 30-40 | 13 | 26 |
| 40-50 | 10 | 20 |
| Above 50 | 7 | 14 |

The 120anti-Ku positive sera were studied.50 of them were affected by systemic autoimmune diseases, whereas we did not have any clinical notice of threesubjects.

**Table 2 Clinical diagnosis of 50 patients with anti-Ku antibodies**

| **Clinical parameter** | Number of patients | **%** |
|---|---|---|
| **Overlap syndrome** | 13 | 26 |
| PM/SSc | 9 | 18 |
| DM/SSc | 2 | 4 |
| PM/SLE | 2 | 4 |
| **UCTD** | 16 | 32 |
| **SLE** | 9 | 18 |
| **Primary SS** | 6 | 12 |
| **PM** | 4 | 8 |
| **SSc** | 1 | 2 |
| **RA** | 1 | 2 |

All 50 anti-Ku positive patients were affected by systemic autoimmune diseases, mainly represented by UCTD in nine cases (32%) and overlap syndromes in eight cases(26%),including PM or Dermatomyositis (DM)/SSc in 9 cases and PM/SLE in 2 case. Additional 9 subjects showed a diagnosis of SLE, 6 were affected by primary SS, 4 byPM whereasSScandRAweredetectedin2patienteach (Table2).
Considering the total systemic autoimmune diseases followed by our Centre, anti-Ku antibodies are detected in 12 SSc patients (11 in overlap with PM/DM and one isolated) out of 120 total SSccases (10%) and in 11 SLE (9 isolated and 2 case in overlap with PM) out of 120 total SLE cases (9.17%). In addition, they were found in nine UCTD patients out of 120(13.33%) and more rarely in primary SS and RA .

**Table 3** Clinical features in 50patients with anti-Kuantibodies

| Clinical features | N=50 | % |
|---|---|---|
| Arthralgias | 40 | 80 |
| Raynaud's phenomenon | 32 | 64 |
| Arthritis | 24 | 48 |
| Xerostomia | 31 | 62 |
| Fatigue | 24 | 48 |
| Interstitial lung disease | 20 | 40 |
| Xerophtalmia | 19 | 38 |
| Myalgias | 21 | 42 |
| Myositis | 14 | 28 |
| Sclerodactyly | 13 | 26 |
| Dyspnoea | 11 | 22 |
| Dysphagia | 13 | 26 |

Articular symptoms (subjective arthralgiasand poly- arthritis) and Raynaud's phenomenon represents the main clinical features observed in our series, detected in 80%, 48% and 64% of patients respectively. In addition, xerostomia and xerophtalmia were reported in 62% and 19patients 38%, and about 28%of subjects showed myositis (Table 2). Pulmonary interstitial disease was detected in 20cases (40%) with a severe and progressive reduction of DLCOin20 patients(40%)and neutrophilicalveolitisin ten. Pulmonary hypertension was recorded in 5cases. Most of patients with pulmonary involvementshowedadiagnosis of PM,SScorPM/SScoverlapsyndrome(11cases),whereastheotherswereaffected by UCTD (six cases), RA and primary SS (one case, each).

**Table 4** Immunological features in 50 patients with anti-Ku antibodies

| | N= 50 | % |
|---|---|---|
| ANA | 50 | 100 |
| Anti-dsDNA | 16 | 32 |
| Anti-Ku w/o other anti-ENA Anti-Ku + other anti-ENA | 36<br>14 | 72<br>28 |
| Anti-Ro/SSA | 7 | 14 |
| Anti-Ro + anti-La | 4 | 8 |
| Anti-Ki | 1 | 2 |
| Anti-Ro + anti-Ki | 2 | 4 |
| Reduced C3 | 12 | 24 |
| Reduced C4 | 9 | 18 |

Mild haematological features, namely leucopenia and thrombocytopenia, were detected in a few patients (10 and 5 cases respectively), mainly affected by SLE or primary SS. Elevated erythrosedimentationrate and C reactive protein were observed in 70% and 30% of cases, whereas polyclonal hypergamma- globulinaemiawaspersistentlydetectedin26subjects (52%).

Immunological features were reported in Table 4: all the patients showed very high titre ANA by IFI on HEp2 cells, with a fine nuclear speckled pattern in 25 sera and a nuclear speckled with homogeneous nucleolir staining in the remaining 25 sera.

Anti-Ku were detected in 36 sera as single anti- ENAspecificity(72%),whilenineserashowedmultiple anti-ENA antibodies, namely anti-Ku with anti- Ro/SSA (globally in 13 cases), with anti-La/SSB (4 cases),

with anti-Ki antibodies (globally in 3 cases). In addition, anti-dsDNA antibodies were detected in 16 sera (32%), whereas anti-cardiolipin and anti-β2GPI antibodies were found in 26% and 22% of casesrespectively.

**Table 5Comparison of clinical diagnosis between 21patients with isolated anti-Ku (without anti-dsDNA or other anti-ENA specificities) and29 patientswith multipleanti-nuclear specificities (anti-dsDNA or other anti-ENA)**

| **Parameter** | Isolated anti-Ku n = 21(42%) | Anti-Ku associated with other ANA n = 29 (58% |
|---|---|---|
| **Overlap syndrome** | | |
| PM/SSc | 6 | 5 |
| PM/SLE | 1 | 1 |
| **UCTD** | 10 | 6 |
| **SLE** | 0 | 9 |
| **Primary SS** | 0 | 6 |
| **PM** | 2 | 2 |
| **SSc** | 1 | - |
| **RA** | 1 | - |

The clinical diagnosis in the two groups of patients is reported in Table 5. As expected, a diagnosis of SLE and primary SS were reported exclusively in patients with multiple autoantibodies (P = 0.03 and P = 0.08 respectively); by contrast, overlap syndromes and UCTD are equally distributed in the two groups. Notably, in the three cases of PM, SSc as well as in five cases of overlap syndromes and UCTD, anti-Ku antibodies were the sole anti-nuclear specificity and, therefore, can represent the immunological marker of disease.

## IV. DISCUSSION

The presence of anti-Ku antibodies in the study of Rozman et al.[17] was reported to be associated with synovitis, joint contractures, and clinical features of myositis, and negatively associated with vascular manifestation of disease.In our study 50 anti-Ku positive patients were affected by systemic autoimmune diseases, mainly represented by UCTD in nine cases (32%) and overlap syndromes in eight cases(26%),including PM or Dermatomyositis (DM)/SScin 9 cases and PM/SLE in 2 case. Additional 9 subjects showed a diagnosis of SLE, 6 were affected by primary SS, 4 byPM whereasSScandRAweredetectedin2patientseach. Considering the total systemic autoimmune diseases followed by our Centre, anti-Ku antibodies are detected in 12 SSc patients (11 in overlap with PM/DM and one isolated) out of 120 total SSc cases (10%) and in 11 SLE (9 isolated and 2 case in overlap with PM) out of 120 total SLE cases (9.17%). In addition, they were found in nine UCTD patients out of 120(13.33%) and more rarely in primary SS and RA.

A similar study conducted by Reeves et al. reported on levels of antibodies against Ku p70 and Ku p80 longitudinally over a period of 70 months in sera of patients with SLE (n = 2), mixed connective tissue disease (n = 1), and Sjögren syndrome (n = 1). Their study suggested that anti-Ku p70/anti-Ku p80 antibodies are generated by a selective antigen-driven mechanism; however, polyclonal activation also frequently accompanied autoantibody production.[18] Yaneva and Arnett examined anti-Ku p70/anti-Ku p80 antibodies with quantitative immunoblotting and found that all positive sera (from mixed ethnic patients with SLE (n = 13), SSc (n = 9), myositis (n = 2), and Sjögren syndrome (n = 2)) had antibodies against Ku p80, and only one serum (from a dermatomyositis patient) did not react with Ku p70. Only anti-Sm antibodies appeared to be associated with anti-Ku antibodies.[19] Ogawa-Momohara*etal.* which reported the clinical phenotype of patients with anti-Ku autoantibodies and conclude that systemic lupus erythematosus(SLE) and myositis overlap is rare in patients with this antibodyreactivity.[20]Ho et al9 described 159 anti-Ku positive patientsso far with the following diagnoses: overlapsyndrome in 34%, SLE in 28%, idiopathic inflammatorymyositis in 4%, SSc in 14% and otherdiseases in 20%.[21]

In our study Articular symptoms (subjective arthralgiasand poly- arthritis) and Raynaud's phenomenon represents the main clinical features observed in our series, detected in 80%, 48% and 64% of patients respectively. In addition, xerostomiaand xerophtalmiawere reported in 62% and 19 patients 38%, and about 28% of subjects showed myositis. Articular and muscular features, Raynaud's phenomenon and sicca were frequently found associated with anti-Ku by previous reports.[22,23]Common features of anti-Ku positivepatients described by Cooley et al andFrancescini et al (reported in undifferentiatedconnective tissue diseases, PM/SSc,

SLE/SSc/PMand SLE/PM overlaps; SSc, primary Sjogrensyndrome,SLE and rheumatoid arthritis) were skinthickening, Raynaud phenomenon, muscular andjoint involvement and oesophageal reflux.[24,25]

## V. CONCLUSION

We conclude that the anti-Ku antibodies are found in different systemic autoimmune diseases and frequently associated with myositis and interstitial pulmonary involvement. Anti-Ku antibodies are usually detected in association with other serological markers in SLE and pSS, while they could occur isolated in SSc and PM

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