Immune-mediated necrotizing myopathies and interstitial lung disease are predominant characteristics in anti-Ku positive patients with idiopathic inflammatory myopathies

We read an interesting study by Spielmann *et al* conducted on a single-centre large French cohort, which identified that anti-Ku autoantibodies were effective biomarkers for two distinct connective tissue diseases (CTDs): anti-Ku-positive patients with elevated serum creatine kinase (CK) levels had a high risk for developing interstitial lung diseases (ILD), while anti-Ku-positive patients with anti-double-strand DNA were at high risk for developing glomerulonephritis.[1] Anti-Ku autoantibodies are associated with various CTDs, such as systemic lupus erythematosus, systemic sclerosis, idiopathic inflammatory myopathies (IIM), mixed CTDs, Sjögren's syndrome, and rheumatoid arthritis. However, few studies have focused on the distinguishing features, especially the pathological features of IIM patients with isolated anti-Ku and anti-Ku coexistence with myositis-specific autoantibodies (MSA).

Here, we retrospectively investigated the characteristics of 1214 IIM patients with anti-Ku autoantibodies, all fulfilling the Bohan & Peter criteria for IIM and admitted to the Department of Rheumatology at China-Japan Friendship Hospital from January 2008 to July 2019. Anti-Ku autoantibodies were detected by line immunoassay (EUROLINE, Germany) and ELISA assay (Enzyme-linked Biotechnology, China) in the sera of 156 patients with anti-nuclear antibodies of titres≥1/160 showing fine speckled patterns on immunofluorescence assay of HEp-2 cells. Finally, 21 patients were confirmed to be anti-Ku-positive by line immunoassay and ELISA assay. Meanwhile, MSA and anti-3-hydroxy-3-methylglutaryl-CoA reductase autoantibody levels in the sera of anti-Ku-positive patients were measured using line immunoassay (EUROLINE, Germany) and ELISA assay (Raybiotech, China). Muscle biopsy was performed in 13 of 21 anti-Ku-positive patients.

The incidence of anti-Ku autoantibodies was 1.73% in our IIM cohort. Twenty out of 21 patients were women. The average age of onset was 42.60±14.35 years. Eight patients were diagnosed with dermatomyositis (DM), 11 with polymyositis (PM), and two overlapping with SSc. Eleven patients (52.4%) showed isolated anti-Ku antibodies, the others (47.6%) coexistence of anti-Ku with MSA. Skin involvement was less common among patients with isolated anti-Ku than that among patients showing coexistence of anti-Ku and MSA (18.2% vs 70%, p=0.03). ILD presented in 76.2% of anti-Ku-positive IIM patients, consistent with the high frequency of ILD reported in previous studies.[1 2] Although there was no significant difference in the incidence of ILD between patients with isolated anti-Ku and anti-Ku coexistence with MSA, patients with isolated anti-Ku had a lower mean percentage of predicted value for FVC and DLco than those with coexistence of anti-Ku and MSA(74.05%±12.84% vs 93.21±18.54%and 59.61±15.41% vs 76.03±14.15%, p=0.035and 0.049, respectively). Increased CK level was observed in 90.9% (10/11) of patients with isolated anti-Ku and 50% (5/10) of those with coexistence of anti-Ku and MSA (table 1).

In the previous studies on French and Japanese cohorts, the musculoskeletal histopathological performance of only 22 IIM patients with anti-Ku-positive was described.[3–5] The main pathological features were muscle fibre necrosis (18/22, 81.8%) and major histocompatibility complex (MHC) class I expression (16/19, 84.2%). In our cohort, 6 of 7 patients with isolated anti-Ku presented typical immune-mediated necrotizing myopathy (IMNM)-like pathological features with predominantly necrotic muscle fibre and CD68$^+$ macrophage endomysial infiltration in accordance with the 2017 European Neuromuscular Centre (ENMC) criteria for IMNM.[6] However, 1 out of 6 patients with coexistence of anti-Ku and MSA presented with typical pathological features of IMNM. Classical pathologic DM such as perifascicular atrophy and normal pathologic performance were observed in anti-TIF1γ- and anti-MDA5-positive

Table 1 Characteristics of anti-Ku-positive patients with IIM

Features	Isolated anti-Ku (n=11)	Coexistence of anti-Ku and MSA (n=10)
Female	10 (90.9%)	10 (100%)
Age of onset	45.55±16.45	39.00±11.47
Duration(months)	12(3,72)	29(4,60)
Diagnosis		
DM	2 (18.2%)	6 (60%)
PM	8 (72.7%)	3 (30%)
PM+SSc	1 (9.1%)	0
DM+SSc	0	1 (10%)
MSA		
MDA5	–	3 (14.8%)
NXP2	–	1 (4.8%)
TIF1γ	–	2 (9.5%)
Jo-1	–	1 (4.8%)
PL-12	–	1 (4.8%)
PL-7	–	1 (4.8%)
SRP	–	1 (4.8%)
MAA		
Ro-52	1 (9.1%)	5 (50%)
PM-Scl 75/100	0	2 (20%)
Muscle Weakness	8 (72.7%)	8 (80%)
Dysphagia	2 (18.2%)	5 (50%)
Neck weakness	1 (8.3%)	1 (10%)
Myalgia	6 (54.5%)	4 (40%)
Skin involvement*	2 (18.2%)	7 (70%)
Raynaud's phenomena	3 (27.3%)	2 (20%)
ILD	8 (72.7%)	8 (80%)
FVC% of predicted value†	74.05±12.84	93.21±18.54
DLco% of predicted value‡	59.61±15.41	76.03±14.15
Arthritis	3 (25%)	2 (20%)
Cancer	0	0
Increased CK	10 (90.9%)	5 (50%)
Pathological pattern	n=7	n=6
IMNM	6	1(anti-PL-7 positive)
pDM	0	2(anti-MDA5 and -TIF1γ positive)
NSM	1	1(anti-Jo-1 positive)
Normal	0	2(anti-MDA5 and -TIF1γ positive)

FVC and DLco value were available for 8 patients with isolated anti-Ku and 7 patients with anti-Ku coexistence of MSA.
*P=0.03.
†P=0.035.
‡P=0.049.
CK, creatine kinase; DLco, carbon monoxide diffusion capacity; DM, dermatomyositis; FVC, forced vital capacity; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathie; MAA, myositis-associated autoantibodies; MSA, myositis-specific autoantibodies; NSM, non-specific myositis; pDM, pathologic DM; PM, polymyositis; SSc, systemic sclerosis.

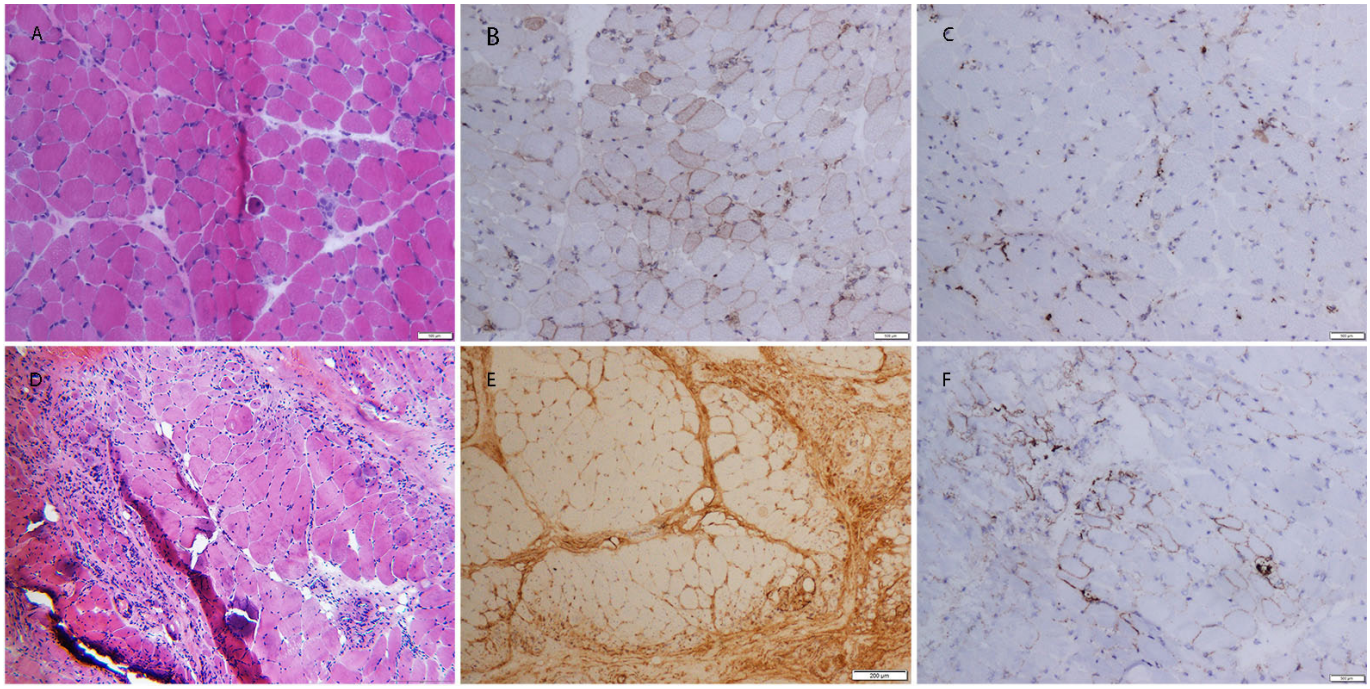

Figure 1 H&E and immunohistochemistry staining of muscle specimens in anti-Ku-positive patients with idiopathic inflammatory myopathies (IIM). A-C, F IIM patient with isolated anti-Ku: Muscle fibre necrosis, myophagocytosis and regeneration(A), sarcolemmal MHC-I expression(B), $CD68^{+}$ cells scattered endomysial infiltration(C), sarcolemmal membrane attack complex(C5b-9) expression(F). D-E, dermatomyositis patient with anti-Ku coexistence of anti-TIF1γ: perifascicular atrophy(D), sarcolemmal MHC-I expression in perifascicular muscle fibre(E).

patients, respectively. In addition, 1 patient with coexistence of anti-Ku and anti-Jo-1 was diagnosed with non-specific myositis according to the 2004 ENMC classification criteria for IIM(table 1, figure 1).[7]

In conclusion, the presence of anti-Ku autoantibodies is rare among IIM patients. Concomitant ILD and elevated CK level are common features of anti-Ku positive patients. However, the clinical and pathological characteristics are distinct in patients with isolated anti-Ku and those with coexistence of anti-Ku and MSA. Skin rash is more common in patients with coexistence of anti-Ku and MSA, while severe ILD and IMNM are common in patients with isolated anti-Ku. Further studies on the characteristics of anti-Ku-positive IIM using larger cohorts are warranted.

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