Anti-RNP antibodies delineate a subgroup of myositis: A systematic retrospective study on 46 patients

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Inflammatory myopathies are a heterogeneous group of autoimmune diseases ranging from muscle-specific diseases to systemic disorders. Myositis can occur as a specific entity or as a part of a spectrum of non-specific connective tissue disorders, including mixed connective tissue disease and systemic lupus erythematosus. Myositis-specific antibodies (MSAs) or non-specific/associated antibodies (MAAs) are autoantibodies frequently described with myositis. Presence of MSA allows to create homogeneous patient subgroups [1]. Nevertheless, the potential ability of MAAs to individualize homogenous subgroups of myositis remains unknown. Anti-U1 small nuclear ribonucleoprotein particle (RNP) antibodies are among the most prevalent MAAs (approximately 15%) [2]. Despite its relatively frequent prevalence, anti-RNP antibody-positive (RNP^+) myositis patients have been poorly described [3–5]. We analyze accurately the anti-RNP+ clinical phenotype, including muscle (with pathological analysis) and extra-muscle manifestations, and compare to myositis without RNP antibodies (anti-RNP-).

This international (French-Japanese) multicentric retrospective study included patients diagnosed with myositis accordingly to Bohan and Peter criteria [6] and anti-RNP antibody positivity. The anti-RNP-control cohort included myositis patients excepted those with inclusion body myositis (because of its very distinct phenotype [7]). Anti-RNP+ patients were defined based on positive RNA immunoprecipitation as previously described [8]. Muscle samples were analyzed by two independent experts in myopathology (S.L. and A.U.). Unsupervised descriptive methods on anti-RNP+ patients or on the global cohort of myositis patients (anti-RNP+ and anti-RNP-) were performed as previously reported [7]. Multiple comparison correction for bivariate analysis was controlled by Benjamini-Hochberg procedure. Multivariate analysis was described with the adjusted p value of the V-test if available. A p-value $\leq .05$ was considered significant.

Anti-RNP+ patients (n = 46; 20 French and 26 Japanese) were predominantly female (83%) with a mean age of 53 years [43–67]. Muscular and extramuscular manifestations are described in Table 1. Anti-RNP+ patients were diagnosed with mixed connective tissue disease (37/46, 80%) or systemic lupus erythematosus (9/46, 20%). > 90% of anti-RNP+ patients had proximal weakness that was frequently severe. The CK levels were high (2395 [999–4382] UI/L) and 10/46 (22%) patients had CK levels higher than 7000 UI/L.

The predominant lesions on muscle biopsy were myofiber necrosis and/or myofiber regeneration (Fig. 1), sarcolemmal C5-b9 deposits and positive membranous diffuse staining of major histocompatibility complex-class I (MHC-I). Unsupervised hierarchical analysis of 207 myositis patients (anti-RNP- n = 174 and anti-RNP+ n = 33) identified four different clusters. Cluster 1 consisted of patients with mainly an anti-synthetase syndrome with anti-Jo1 antibody. Cluster 2 included 70% of all anti-RNP+ patients by positioning RNP+ variable (V test p value < .0001). Raynaud phenomenon (16/17, 94%, V test p < .0001) and puffy hands (16/17, 94%, V test p < .0001) were the two main associated symptoms. Cluster 3 contained a majority of patients with immune necrotizing myopathies. Interestingly, this cluster gathered the remaining anti-RNP+ patients, highlighting the phenotype proximity of these two entities. Finally, in cluster 4 patients had a dermatomyositis pattern with the classical dermatomyositis skin rash.

Six variables/predictors were significantly associated to the presence of anti-RNP+: absence of MSAs (OR 0.096, 95% CI 0.023–0.332), absence of muscle inflammation (OR 0.188, 95% CI 0.05–0.617), absence of typical dermatomyositis skin rash (OR 0.069, 95% CI 0.006–0.398), less disturbed pulmonary function tests (OR 0.126, 95% CI 0.026–0.475), presence of puffy hands (OR 11.136, 95% CI 1.489–123.405) and Raynaud phenomenon (OR 4.805, 95% CI 1.117–24.127).

Clinico-pathological patterns of anti-RNP+ myositis consisted of severe necrotizing myositis associated with frequent extra-muscular manifestations associating Raynaud phenomenon and/or puffy hands, arthralgia and/or interstitial lung disease. Anti-RNP+ myositis is a separate entity that differentiates them from the well-known subgroups of myositis (dermatomyositis, anti-synthetase syndrome and immune-mediated necrotizing myopathies [9]) even if this entity shares some common features with IMNM especially in the pathological field [10]. The extra-muscular manifestations of anti-RNP+ myositis patients are those of the spectrum of mixed connective tissue disease or systemic lupus erythematosus.

We also found that a minority of anti-RNP+ patients presented MSAs and when present they consisted primarily of anti-SRP and anti-OJ antibodies. It must be highlighted that in these cases, patients presented both phenotypes. If anti-RNP antibody delineates a subgroup of patients, it must be emphasized that standard immune-assay for anti-RNP detection bring frequent false-positive results. Since immunoprecipitation cannot be performed routinely, the results of stan-

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Table 1
Muscular and extra-muscular features of anti-RNP$^+$ patients.

	N (IQR or %)
Age at diagnosis (years)	48 (35–62)
Females	38/46 (83%)
Extra-muscular features	
Raynaud phenomenon	23/46 (50%)
Puffy hands/sclerodermic hands	14/46 (30%)
Arthralgia	21/28 (75%)
Arthritis	8/22 (36%)
Dyspnea	17/46 (37%)
Pulmonary hypertension	5/17 (29%)
Interstitial lung disease	18/43 (42%)
Pleural effusion	1/40 (2.5%)
FVC (%)	80 (59–102)
DLCO (%)	56 (44–67)
Pericardial effusion	8/25 (32%)
LVEF (%)	70 (66–70)
Esophageal impairment	17/28 (61%)
Muscular features	
Clinical	
Proximal weakness	41/46 (89%)
Distal weakness	13/45 (29%)
Manual muscle testing (five MRC score)	3 (3–4)
CK level (UI/L)	2395 (999–4382)
Myogenic syndrome (EMG)	31/37 (84%)
Pathological	
Necrosis/regeneration	35/42 (83%)
Internal nuclei ≥5%	23/42 (55%)
Perivascular inflammatory infiltration	16/42 (38%)
MHC-I-positive muscle fibers	36/42 (85%)
Diffuse	27/42 (64%)
Scattered	6/42 (14%)
Peri-fascicular enhance	3/42 (7%)
Sarcolemmal deposits of C5-b9	20/38 (53%)
Peri-fascicular dominance	4/38 (11%)
Auto-antibodies	
Myositis-specific antibodies	12/46 (26%)
Anti-SRP	5/12 (42%)
Anti-OJ	4/12 (33%)
Anti-JO1	1/12 (8%)
Anti-MDA5	1/12 (8%)
Anti-HMGCR	1/12 (8%)
Myositis-associated antibodies	24/46 (52%)
Anti-Sm	7/46 (15%)
Anti-native DNA	5/46 (11%)
Anca	2/46 (4%)
Anti-SSA 52/60	14/46 (30%)
Anti-SSB	1/46 (2%)
Anti-Ku	3/46 (7%)

dard immunoassay must be interpreted with the clinico-pathological data as well as with the immunofluorescence pattern of anti-nuclear antibody detection.

To conclude, anti-RNP + myositis appears to be a distinct subgroup of idiopathic inflammatory myopathies. However, some anti-RNP + patients are close to IMNM. This finding emphasizes that the importance of auto-antibodies in myositis classification is not limited to myositis-specific antibodies.

Declaration of Competing Interest

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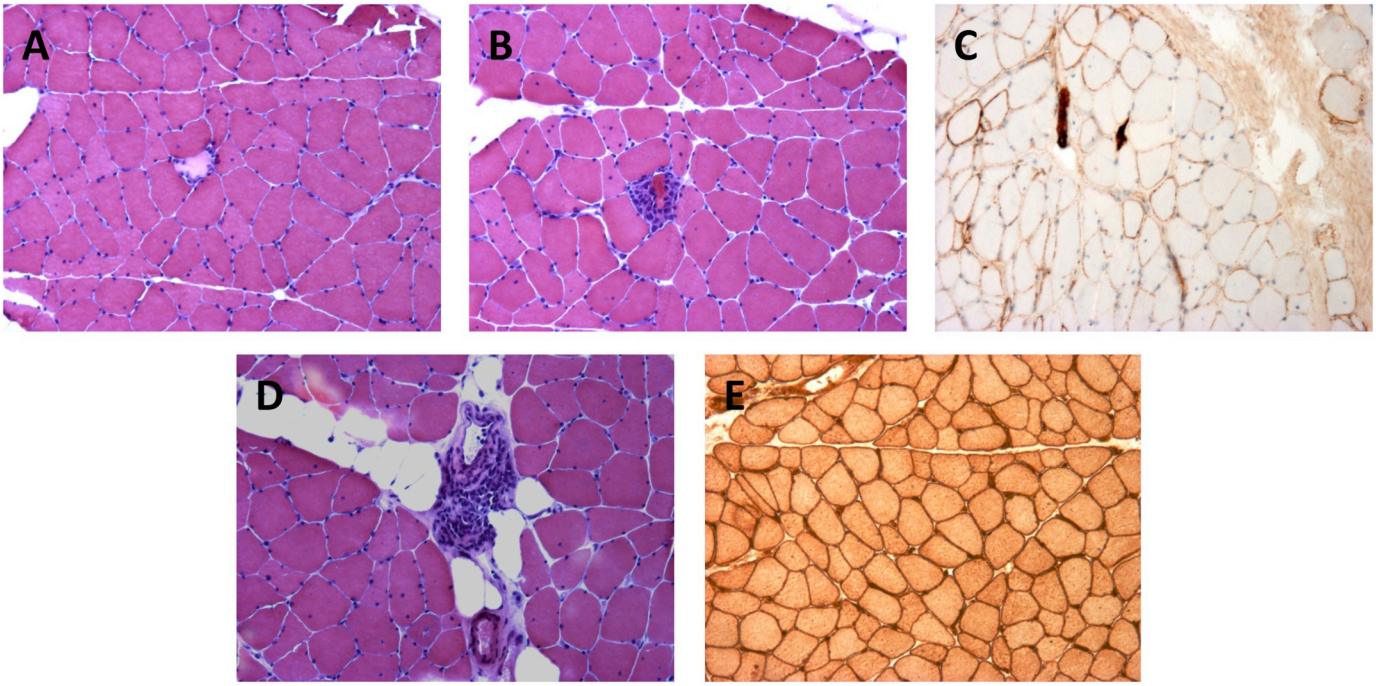

Fig. 1. Pathological features of anti-RNP+ myositis. Necrotic muscle fibers (A) and myophagocytosis (B) are observed in an anti-ribonucleoprotein (RNP)$^{+}$ patient, without any specific distribution (dystrophin 2 immunohistochemical staining eosin counterstaining). Deposits of membrane attack complex (C5b-9) on the sarcolemma of myofibers (C). Inflammatory infiltrates are localized in perivascular areas (D). Major histocompatibility complex-1 (MHC-1) expression is diffusely positive (E) (MHC-1 immunohistochemical staining).

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