Clinical Characteristics of Immune-Mediated Necrotizing Myopathy with Autoantibodies Recognizing the Signal Recognition Particle: A Retrospective Study of a Chinese Cohort

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Research Article

Abstract

Objective: Immune-mediated necrotizing myopathy (IMNM) with autoantibodies recognizing the signal recognition particle (SRP) patients tend to have prominent proximal weakness and infrequent extra-muscular involvement, especially interstitial lung disease (ILD). However, we reported a Chinese cohort of anti-SRP IMNM patients with relatively more frequent ILD.

Methods: Anti-SRP IMNM patients from September 2016 to November 2019 were included according to the most recent European Neuromuscular Center criteria for IMNM. All sera for anti-SRP autoantibody and other myositis-related autoantibodies detection were obtained before the treatment initiation. Muscle strength, coexisting autoimmunity, complications including ILD, treatment and follow-up outcomes were also recorded. Univariate logistic regression was performed to determine variables predicting bad outcomes.

Results: Of 271 patients with idiopathic inflammatory myopathy tested, we diagnosed 23 (8.5%) patients with anti-SRP IMNM. Muscle weakness was presented in 23 patients (100%) and generally worse in the lower limbs. ILD was observed in 50% anti-SRP IMNM patients. Predictor of bad outcomes identified by univariate logistic regression analysis was complicated ILD (odds ratio, 3.8).

Conclusion: ILD tends to be more frequent in this Chinese anti-SRP IMNM cohort from Hunan province. Complicated ILD represents a risk factor for bad outcomes for anti-SRP IMNM.

Introduction

Over the past decades, immune-mediated necrotizing myopathy (IMNM) has been recognized as a category of idiopathic inflammatory myopathy (IIM) characterized by myofiber necrosis with minimal inflammatory cell infiltrate [1]. IMNM is a rare disease with an estimate of 6/1,000,000 annual incidence [2]. It is regarded as a different subtype from other IIM including polymyositis, dermatomyositis and inclusion body myositis [3]. The heterogeneous pathogenesis of IMNM includes autoantibody-mediated, drug-induced and paraneoplastic disease, along with overlap syndrome and viral infections [4–6]. It is of clinical importance to identify autoantibodies of patients because each autoantibody is closely associated with certain clinical manifestations.

The autoantibodies recognizing signal recognition particle (SRP) and anti 3-hydroxy-3-methylglutaryl-coenzymeA reductase (HMGCR) antibody are most commonly detected in IMNM. SRP is a ubiquitous cytoplasmic RNA protein consisting of 7S RNA and 6 proteins with molecular weights of 9, 14, 19, 54, 68 and 72-kDa, which collectively mediates the translocation of newly synthesized proteins across the endoplasmic reticulum. Anti-SRP antibodies were first discovered in the serum of patients with clinical polymyositis by the presence of 7S RNA detected by RNA immunoprecipitation [7]. Meanwhile, immunoblot for the 54-kDa protein subunit of the SRP has also been used to screen serum samples for anti-SRP antibodies as markers of IMNM, which was considered as a new entity within the polymyositis spectrum

[8]. Studies have demonstrated that anti-SRP IMNM is distinct from other myopathies, and characterized by markedly elevated serum creatine kinase levels and rapidly progressive proximal muscle weakness leading to significant disability [9]. Meanwhile, extra-muscular clinical manifestations associated with anti-SRP antibody tend to be less frequent than in other subsets of IIM [10,11]. Specifically, interstitial lung disease (ILD) occurs in just 10%-30% of patients with anti-SRP myopathy in Japan and Europe [12,13]. Strikingly, however, we find ILD in anti-SRP IMNM tends to be more frequent in Chinese population.

The purpose of the present study was to elucidate the common and distinct clinical features of IMNM associated with anti-SRP autoantibody among 23 patients through a single center study in a Chinese cohort. We also compared patient survival in anti-SRP IMNM patients with ILD and without ILD.

Results

Demographics

Of the 271 patients with IIM, we diagnosed 23 (8.5%) patients as anti-SRP IMNM, all having 2 + or 3 + degree of anti-SRP autoantibody. The demographics of these anti-SRP IMNM patients are shown in Table 1. Frequencies of myositis-specific or myositis-associated autoantibodies are shown in Supplement Table 1. Median age at symptom onset was 53 years (range, 23–69 years); 14 patients (61%) were women. Median symptom duration at diagnosis was 6 months (range, 1–47 months).

Clinical features

All clinical features of the 23 patients are recorded in Supplement Table 2 ~ Supplement Table 4. A chief complaint of muscle weakness was presented in 23 patients (100%) and generally worse in the lower limbs. Other symptoms found in the 23 anti-SRP IMNM patients included myalgia (6 patients), dyspnea (4 patients), dysphagia (3 patients), cough (7 patients) and fever (1 patient). Coexisting features of rheumatic diseases (outside of the lungs) were infrequent and reported for 3 of 23 patients (skin rash: 1, Raynaud's phenomenon: 1, dry eyes and dry mouth: 1). HRCT was performed in 22 patients (one patient refused HRCT scanning) and ILD was observed in 50% (11/22) of the anti-SRP IMNM patients, most of whom had nonspecific interstitial pneumonia, and the others had usual interstitial pneumonia. Of the 23 patients for whom further information was available, no malignancy and history of statin were found.

As depicted in Supplement Table 1, 22 patients detected with 3 + degree of anti-SRP antibody, and only 1 patient with 2 + anti-SRP. Other autoantibodies detected in the 23 SRP antibody positive patients included 9 patients with anti-Ro-52, 8 patients with ANA, 4 patients with anti-SSA (Ro-60), 2 patients with anti-SSB, 2 patients with RF, 1 patient with weak p-ANCA and 1 patient with anti-Mi-2β. None of the 23 patients had a diagnosis of overlapping diseases such as with SLE, RA, dermatomyositis, polymyositis, myositis with anti-tRNA synthetase antibodies, inclusion body myositis, or antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. However, symptoms of dry eyes and dry mouth and positive autoantibodies (anti-SSA, anti-SSB) suggestive of Sjogren's syndrome were present in one patient.

The EMG findings showed myogenic changes, including myopathic motor unit potentials and prominent spontaneous activity in proximal muscles in all of the 22 patients examined (one patient refused to do the EMG). Muscle biopsy was performed in four patients. Common histological features included necrosis and regeneration of muscle fibers, with no or little lymphocyte infiltration (Fig. 1a). Scanning electron microscopy (Fig. 1b) demonstrated lysis of muscle fibers and deposition of lipid droplets in muscle fibers. Lung HRCT indicated ILD (Fig. 1c) in some patients. The major HRCT findings are bilateral and symmetrical ground glass opacities with subpleural predominance, coarse reticular patterns, and sometimes honeycombing appearances. Lung histology of one patient with anti-SRP IMNM and ILD (Fig. 1d) showed fibroblastic proliferation of alveolar septum and infiltration of lymphocytes.

Serum CK before the treatment was significantly elevated (more than 1000 IU/L) in 87% (20/23) myositis patients with anti-SRP autoantibodies, ranging from 2980.2 IU/L to 17777.5 IU/L. The distribution of decreased serum CK ($p < 0.0001$), Mb ($p = 0.0005$) and LDH ($p = 0.25$) levels (Fig. 2) paralleled clinical improvement, indicating treatment efficacy.

Treatment and outcomes

Combination therapy most commonly included corticosteroids (MPred) and a steroid-sparing agent (70%, 16/23), or triple therapy with corticosteroids (MPred), IVIG, and a steroid-sparing agent (26%, 6/23). AZA was the most commonly used steroid-sparing agent (83%, 19/23). In general, initial corticosteroid therapy included intravenous MPred at 1-2mg*kg^{-1}*day^{-1} for 5–10 days followed by oral corticosteroid, whereas IVIG was dosed at 400mg*kg^{-1}*day^{-1} for 3–5 days. AZA was taken as 1-2mg*kg^{-1}*day^{-1}. Adjustments in corticosteroid and IVIG dose and frequency were based on clinical response. During the follow-up period, 3 patients lost to follow up and 20 patients needed two immunotherapeutic agents (MPred 4–12 mg/day and AZA 50–100 mg/day) as maintaining therapy.

Follow-up (median: 21 months) data were sufficient in 20 patients to determine clinical course. Only one patient was able to discontinue immunotherapy because of complete remission (grade 5). Two patients died (grade 0) from respiratory failure due to ILD and complicated infection during the follow-up. Other outcomes found in the 20 patients with follow up data included grade 1 (0 patients, 0%), grade 2 (4 patients, 20%), grade 3 (5 patients, 25%), grade 4 (6 patients, 30%) and grade 5 (3 patients, 20%). In total, good outcomes occurred in 70% (14/20) patients. Weakness relapse and increase in serum CK level occurred in five patients (25%, 5/20) whose immunotherapy was tapered or discontinued, requiring resumption of immunotherapy.

Predictor of bad outcomes (grade 0–2) identified by univariate logistic regression analysis was complicated ILD (odds ratio 3.8, $p = 0.05$). The interval between onset and initiation of therapy did not seem to predict outcome, but the number of patients presenting was too small to make a definite conclusion.

Comparison of patients with ILD and without ILD

Among the 23 SRP antibody positive patients in our cohort, we identified 11 with ILD and 11 without ILD (1 patient not evaluated for ILD). Comparative clinical features in anti-SRP IMNM patients without ILD and with ILD are shown in Table 2. The ILD group has significantly more female patients (91% vs 27%, p = 0.008) and lower CK (p = 0.04). The two groups had no difference in anti-SSA, SSB, or Ro-52 antibodies (p = 0.586, 0.476, 0.659). There were 2 deaths among the 20 follow-up patients, and both were in the anti-SRP IMNM group with ILD. No deaths occurred in anti-SRP IMNM without ILD. Those two patients who died had underlying respiratory failure at age 58 and 63 years, respectively (21 months and 12 months, respectively, after onset of myositis). As shown in Fig. 3, cumulative survival among the SRP-positive group with ILD was not significantly different (log rank p = 0.13) from that in the SRP-positive group without ILD.

Discussion

The present study is comprehensive analysis of clinical features of Chinese IMNM patients with anti-SRP autoantibodies, including those with and without ILD. The present study's findings can be summarized as follows: (1) the frequency of anti-SRP autoantibody in patients with idiopathic inflammatory myopathy was 8.5% (23/271); (2) ILD is frequently observed in anti-SRP IMNM patients (11/22) from this Chinese cohort, and (3) complicated ILD (odds ratio, 3.8) was a risk factor for bad outcomes.

Previous studies reported that frequency of anti-SRP autoantibody was 5–10% in patients with idiopathic inflammatory myopathy [14–16]. The frequency of anti-SRP autoantibody in our present study (8.5%) was similar to the previous studies.

The age of onset of IMNM patients is reported usually around 50 and mainly affects females [17]. Most patients have muscle weakness, which affects the lower limbs most severely [11] and markedly elevated serum CK levels [15,18,19]. All those features are consistent with our study. Pinal-Fernandez et al. reported very high serum muscle enzyme levels with a mean peak creatine kinase of 6272 IU/L in anti-SRP IMNM patients [11]. In line with this report, we observed median pre-treatment serum CK values of 7197 IU/L in our cohort.

In myopathy patients with anti-SRP autoantibody, the frequency of ILD has been considered low [20]. In 1990, Targoff reported only one of 10 patients with anti-SRP had interstitial fibrosis, determined either by chest radiograph reading or by the report of the referring physician [15]. Similarly, in a Mayo Clinic's series, ILD was not reported in 54 patients with autoimmune SRP myopathy [17]. In contrast, ILD was observed in 19% of the anti-SRP group by Watanabe [21], supporting another recent analysis of 100 inflammatory myopathy patients with anti-SRP antibody showing that ILD was present in 13% patients [8]. In these patients, the major CT findings are ground glass attenuation which is commonly bilateral and symmetrical with subpleural predominance, irregular linear, reticular opacities and traction bronchiectasis. However, the pathological findings of the lungs have not been described in detail. In rare cases, ILD with anti-SRP-positive myopathy may be severe requiring lung transplantation [22].

Since most previous reports have focused on muscle features, the clinical characteristic of ILD were not well known in patients with anti-SRP autoantibody. Here, we report histologic features of one lung specimen obtained from anti-SRP IMNM patient with ILD: fibroblastic proliferation of alveolar septum and infiltration of lymphocytes. Of note, ILD is more frequently observed in anti-SRP IMNM Chinese patients (50% in our study), and was considered as a risk factor for bad outcomes.

During recent years, more than 15 myositis-specific autoantibodies have been identified. These antibodies may be associated with distinct clinical phenotypes. Some are considered to be positively correlated with ILD, such as anti-synthetase autoantibodies and anti-MDA5 (often rapidly progressive). Among the 23 SRP antibody positive patients in our cohort, we only reported one patient with a diagnosis of Sjogren's syndrome with positive anti-SSA and anti-SSB autoantibodies. The comparative clinical features of anti-SRP IMNM patients with and without ILD showed no difference in other antibodies that maybe associated with ILD including anti-synthetase autoantibodies, anti-MDA5, and anti-Ro-52. Therefore, ILD in the 11 patients we reported was most likely associated with anti-SRP antibody. In previous reports, anti-SRP myositis patients may also have cardiac involvement, including cardiac rhythm or conduction abnormalities as well as cardiac insufficiency in 13%-16% [21,23,24]. However, we did not observe obvious cardiac involvement in this anti-SRP-positive Chinese cohort.

According to the ENMC 2017 guideline [25], first line treatment remains corticosteroids and a steroid-sparing agent. AZA is the preferred agent with a dose of 3mg/kg. Intravenous immunoglobulins may also be needed. In our study, the patients received combination therapy with MPred and a steroid-sparing agent (70%), or triple therapy with MPred, IVIG, and a steroid-sparing agent (26%). AZA was the most commonly used steroid-sparing agent (83%). Among the 21 anti-SRP-positive patients followed up for at least 2 years, only 10 (48%) returned to at least near-full strength [11]. Muscle lesions have been demonstrated to be generally resistant to treatment with corticosteroid and immunosuppressants [26]. However, in our cases without ILD, immunosuppressive therapy was effective, resulting in good outcome in 90% of this subgroup. Although, there are few reports on the treatment for ILD in the setting of SRP antibodies, the improvement of chest radiological findings after corticosteroid therapy and intravenous immunoglobulin therapy was reported in a case report with three cases [27]. Here, we demonstrated relatively poor outcomes for those patients with ILD through Kaplan-Meier analysis. Treatments other than corticosteroids, immunosuppressive agents, and IVIG should be evaluated. Rituximab as B cell depletion therapy [9] or tofacitinib as a Janus kinase inhibitor [28] might be an effective and often life-saving therapy for anti-SRP IMNM patients with ILD.

Regarding overall prognosis, Kao et al. [14] described that the 5-year cumulative survival rate in the SRP-positive polymyositis patients (86%) was not significantly different from SRP-negative polymyositis patients (75%). These results may indicate that the prognosis of the SRP-positive polymyositis patients is not worse compared with the SRP-negative polymyositis patients. In the present study, there were two deaths among the 23 anti-SRP IMNM patients. Both patients were complicated by ILD. However,

cumulative survival among the SRP-positive with ILD group was not significantly different (log rank p = 0.13) from that in the SRP-positive group without ILD.

There were several study limitations. 1) Since muscle weakness is the predominant clinical feature in patients with anti-SRP IMNM, documenting the degree of weakness is a critical aspect of managing these patients. The MRC scale or the transformed Kendall scale has a ceiling effect, such that some patients with weakened strength may still be scored as having normal power (an MRC score of 5). A hand-held muscle strength dynamometer might be an additional choice over using the MRC scale alone [11]. 2) the other limitation is the patient population. Because this study was conducted in a single center, generalization of our results to other populations may not be warranted.

Patients And Methods

Patients

The study was approved by the Institutional Review Board of Second Xiangya Hospital, Central South University (Approval ID: 2020-K011), all research was performed in accordance with relevant guidelines, and written informed consents were obtained from all participants. We collected data of inpatients at the Department of Rheumatology and Immunology, Second Xiangya Hospital of Central South University from September 2016 to November 2019. According to the most recent European Neuromuscular Center (ENMC) criteria for IMNM (2017) [25], patients with (1) elevated serum CK levels, (2) proximal muscle weakness, and (3) anti-SRP autoantibodies can be defined as having "anti-SRP myopathy". While muscle biopsy features and electromyography (EMG) findings may be useful in further characterizing and differentiating patients with anti-SRP myopathy, they are not required for subtyping. The following inclusion criteria were used: (1) chief complaint of weakness; (2) very high serum creatine kinase level with more than 50 times the upper limit of normal, or EMG demonstrating active myopathic units, or biopsy abnormalities that include necrotic fibers with macrophages (no CD8$^+$ cells or vacuoles; deposits of complement on capillaries) [6]; and (3) positive anti-SRP antibody by semiquantitative immunoblotting. Other types of myopathy patients without anti-SRP antibody were excluded. For all patients, the following clinical data were recorded: age, sex, disease onset, symptoms, lung imaging of ILD, EMG findings, treatments provided, and outcomes.

Autoantibody profiles and creatine kinase detection

All sera for autoantibody detection were obtained before the treatment initiation. Autoantibodies to SRP54 (the 54kD subunit of SRP) were measured using a standard immunoblotting protocol [29] (Euroline Myositis Profile 3 immunoline blot). If a serum sample was positive, specific antibodies bound to antigens resulted in bands. The immunoblot with no band was marked as 0; very weak band was marked as (+); weak band was marked as 1+; relatively strong band was marked as 2+; band same as positive control marker was marked as 3+. The program from EUROIMMUN (Lubeck, Germany) provided automotive evaluation of bands, and 2 + ~ 3 + were considered as clinically significant.

The presence of myositis-specific antibodies (MSAs) other than anti-SRP antibodies such as anti-transfer RNA (tRNA) synthetase antibodies (Jo-1, PL-7, PL-12, OJ, EJ), anti-Mi-2α, anti-Mi-2β, anti-TIF1γ, anti-MDA5, anti-NXP2, anti-SAE1 and myositis-associated antibodies (MAAs) such as anti-Ro-52, anti-Ku, anti-PM-Scl100, anti-PM-Scl75 were also detected using the above methods. Meanwhile, autoantibodies related to connective tissue diseases, such as anti-nuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-SSA (Ro-60), anti-SSB, rheumatoid factor (RF), anti-neutrophil cytoplasmic antibody (ANCA) were also identified. The level of creatine kinase (CK), myoglobin (Mb) and lactate dehydrogenase (LDH) before and after treatment were detected.

Muscle strength

The Medical Research Council (MRC) scale was indicated and transformed to Kendall's 0–10 scale [11] for evaluating the strength of muscles in upper-limb and lower-limb. Other possible symptoms including myalgia, skin rash, dysphagia, cough, dyspnea, fever, dry eyes and mouth or Raynaud's phenomenon were also recorded.

Coexisting autoimmunity and complicated Interstitial Lung disease

Coexisting autoimmune diseases, diagnosed according to the established classification criteria for each disease [30–36] were evaluated. ILD was defined by the presence of pulmonary fibrosis seen by high-resolution computed tomography (HRCT)[14]. Imaging manifestations of lung HRCT include thickening of the bronchovascular bundles and interlobular septa, ground glass opacities, coarse reticular patterns, and honeycombing. All the HRCT were evaluated by radiologists the interpreters were blinded to the clinical information.

Biopsy

According to the most recent European Neuromuscular Center (ENMC) criteria for IMNM (2017) [25], the presence of elevated CK levels and proximal weakness is sufficient to diagnose the disease subtype in those patients that are positive for anti-SRP antibodies. Muscle or lung biopsy was only processed for those patients who could not be diagnosed through non-invasive procedures or had treatment-refractory disease.

Treatment

Methylprednisolone (MPred), methotrexate (MTX), azathioprine (AZA), tacrolimus (TAC), cyclophosphamide (CYC), cyclosporine (CyA) and intravenous immunoglobulin (IVIG) encompassed the range of drugs used for treatment of this cohort. Treatment regimens varied between patients, depending on the individual's clinical circumstances.

Follow-up outcomes

Response to treatment was graded as death (grade 0), no improvement (grade 1), mild improvement (grade 2, 1 MRC grade in 1−2 muscle groups, persistently requiring assistance for ambulation and activities of daily living), moderate improvement (grade 3, >1 MRC grade in multiple muscle groups, requiring minimal assistance with ambulation and with activities of daily living), marked improvement (grade 4, symptoms and signs of mild weakness, but no functional limitation), and complete remission (grade 5, no symptoms or signs of weakness), which is modified from Kassardjian et al. [1]. Relapse was also recorded for the re-hospitalized patients. Grade 3−5 were considered as good outcomes; others were marked as bad outcomes.

Statistical analysis

Categorical variables were expressed as percentages and absolute frequencies, and continuous variables were reported as median and interquartile range given small sample sizes. Univariate logistic regression was performed to determine variables predicting bad outcomes, but multivariate regression was not performed because of the small sample size. The variables analyzed were age, sex, anti-Ro-52 autoantibody, laboratory test (CK, Mb, LDH), ILD, lung infection and treatment with 1−2 drugs. To assess differences between anti-SRP IMNM patients with ILD and without ILD, the following analyses were used: categorical variables were compared using the Fisher exact tests and continuous variables using the independent samples Mann-Whitney U tests. Differences in survival were assessed by log rank test. Calculations were performed using the IBM SPSS Statistics v23.0 (Armonk, NY, USA) and GraphPad Prism v8.0 (La Jolla, CA, USA). P values less than 0.05 were considered significant.

Conclusion

ILD in anti-SRP IMNM patients tends to be more frequent in the Chinese population. Complicated ILD is the risk factor for bad outcomes for anti-SRP IMNM, but 70% of patients still reported good outcomes. Further studies are needed to elucidate the underlying disease pathogenesis and the precise role of the anti-SRP autoantibody in this unique subset with both IMNM and ILD.

Declarations

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures
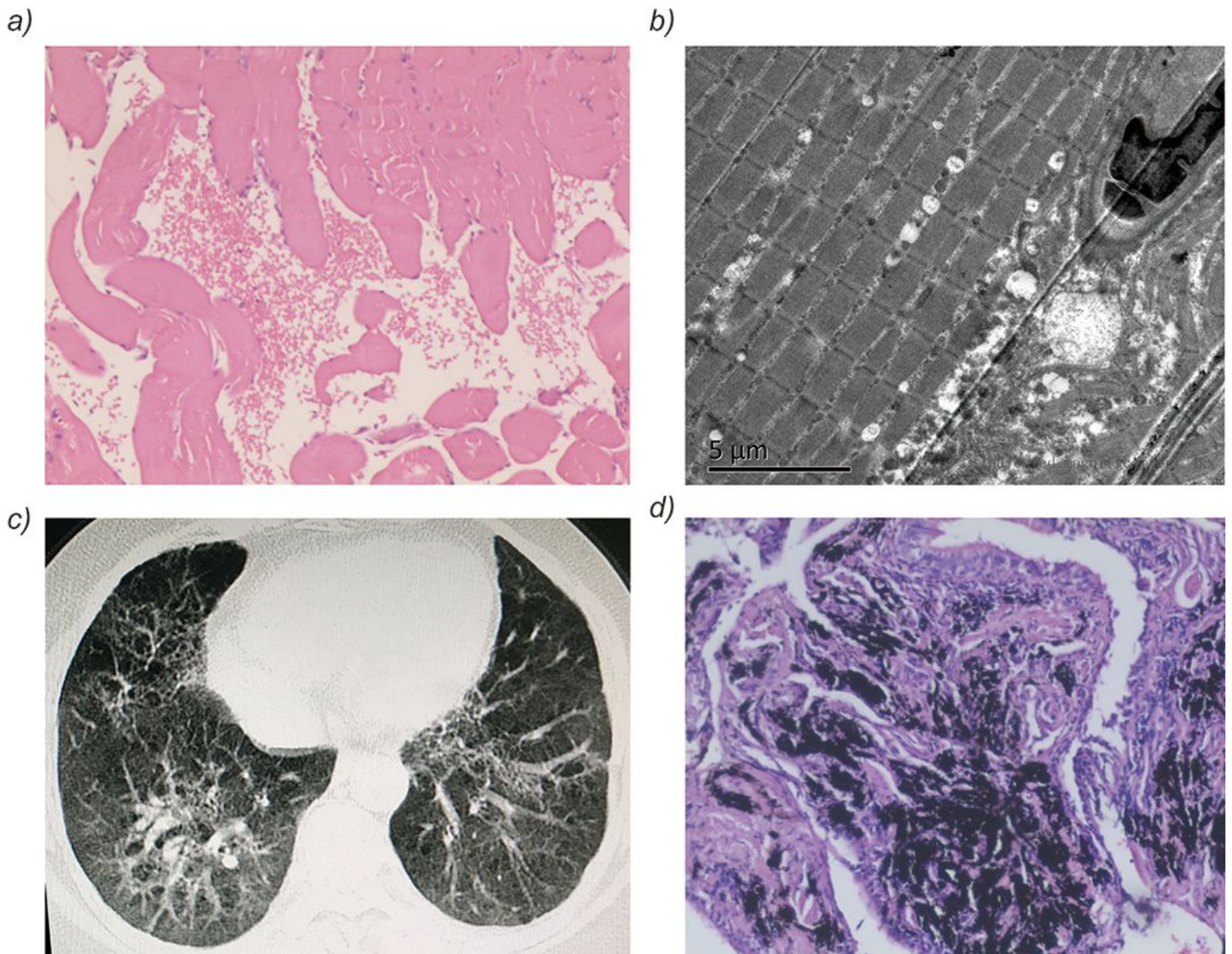
Figure 1

Muscle biopsy (a-b), lung CT (c) and biopsy (d) of anti-SRP IMNM patients with ILD 1a: Muscle biopsy of one patient showed necrosis and regeneration of muscle fibers, with no or little lymphocyte infiltration; 1b: Scanning electron microscopy demonstrated lysis of muscle fibers and deposition of lipid droplets in muscle fibers; 1c: Lung HRCT of one patient showed bilateral and symmetrical ground glass opacities with subpleural predominance, and coarse reticular patterns. 1d: Lung histology of one patient showed fibroblastic proliferation of alveolar septum and infiltration of lymphocytes.
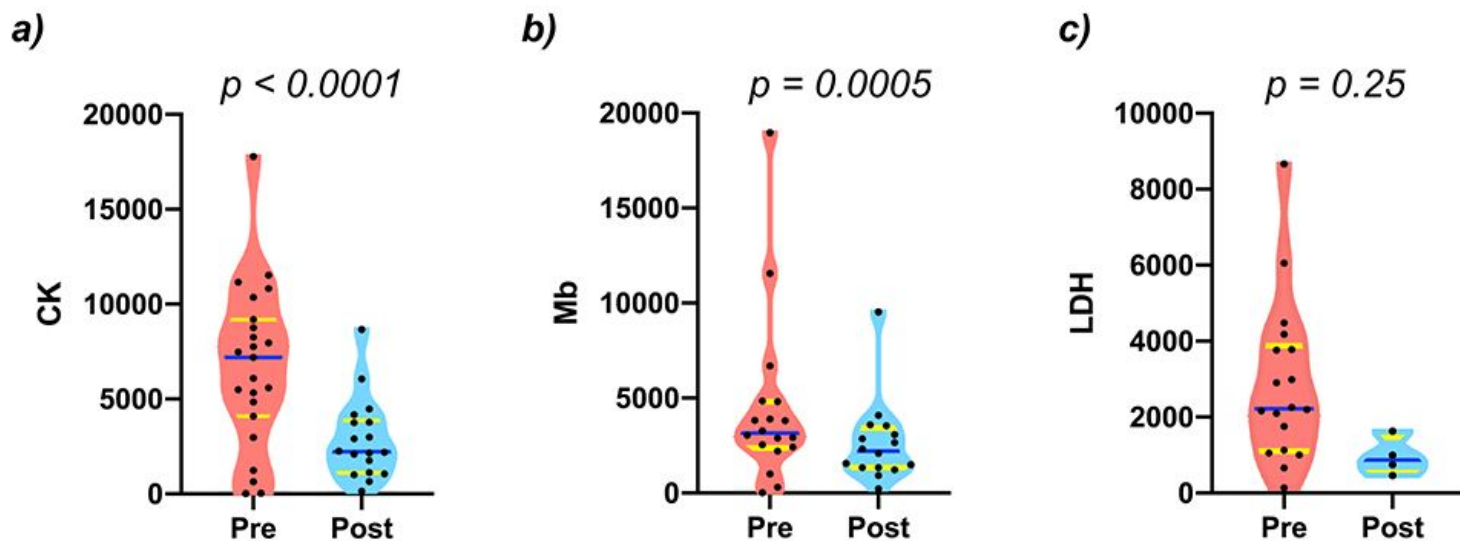
Figure 2

Violin plots of serum CK (a), Mb (b) and LDH (c) levels before treatment (Pre) and after treatment (Post) in anti-SRP IMNM patients
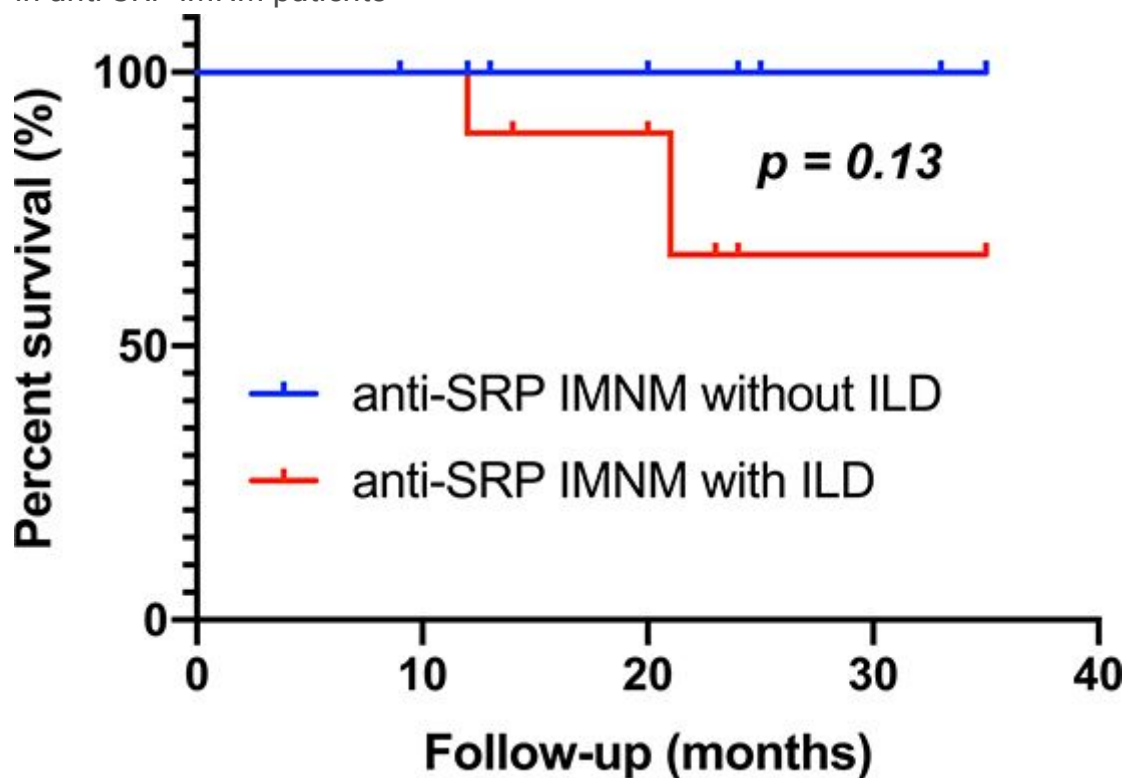

Figure 3

Cumulative survival curves of anti-SRP IMNM patients with ILD and without ILD

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupTables.docx
- Table1.png
- table2.png