


RESEARCH

Open Access



Factors associated with refractory autoimmune necrotizing myopathy with anti-signal recognition particle antibodies

Yawen Zhao, Wei Zhang, Yilin Liu, Zhaoxia Wang and Yun Yuan* 

Abstract

Background: Autoimmune necrotizing myopathy with anti-signal recognition particle antibodies (ANM-SRP) is regarded as refractory myositis, whereby some patients respond poorly to conventional immunosuppression and require B cell depletion treatment. This study aimed to evaluate factors associated with refractory ANM-SRP.

Results: Clinical and pathological data from 48 patients with ANM-SRP were collected. We followed up clinical symptoms and image changes over 12 months. Univariate and multivariate analyses were undertaken to determine the associations between variables of interest and poor response to therapy. Refractory ANM-SRP appeared in 32.5% of patients who showed no or minimal improvement after 12 months of steroid therapy. The clinical risk factors for refractory patients were being male (OR, 19.57; $P < 0.001$), severe muscle weakness (OR, 7.51; $P < 0.001$) and concurrent interstitial lung disease (OR, 39.70; $P < 0.001$). The imaging refractory-related factor was the fatty infiltration rate of thigh muscles over 3 months ($P = 0.022$) and the pathological factor associated with refractory ANM-SRP was the high expression of B cell activating factor receptor (BAFF-R) in muscle ($P = 0.036$).

Conclusion: Being male, severe muscle weakness, concurrent interstitial lung disease, quick development of muscle fatty infiltration and more BAFF-R and B lymphocyte infiltration in muscle indicate a poor response to immunosuppressive therapy in patients with ANM-SRP.

Keywords: Autoimmune necrotizing myopathy, Anti-signal recognition particle antibodies, Refractory myositis, Thigh MRI, B cell activating factor receptor

Background

Autoimmune necrotizing myopathy with anti-signal recognition particle antibodies (ANM-SRP) is a subtype of a group of idiopathic inflammatory myopathies characterized by the presence of anti-SRP antibody in serum [1]. It is often treated as refractory myositis because of its poor response to immunosuppressive agents including glucocorticoids and second-line immunosuppressive therapy [2, 3], especially in patients with other myositis-specific autoantibodies [4, 5] or other autoimmune

diseases [6], often requiring a combination of medications [2, 7]. Japanese studies also used glucocorticoids as basic drugs, 77% of which required additional immunosuppressants [8]. B lymphocyte depletion therapy (rituximab) has been shown to be beneficial in refractory patients, which suggests that the proliferation and differentiation of B lymphocytes play an important role in the pathogenesis of ANM-SRP [3, 9, 10].

Several investigations demonstrated that early-onset disease, severe myasthenia, dysphagia, and muscular atrophy, combined with concurrent interstitial lung disease (ILD) may be risk factors for poor prognosis of ANM-SRP [2, 8]. Additionally, patients with a chronic disease course often show more severe myasthenia

* Correspondence: yuanyun2002@126.com

Department of Neurology, Peking University First Hospital, No. 8 Xishiku Street, Xicheng District, Beijing 100034, PR China



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

symptoms and muscular atrophy, as well as poorer treatment response and prognosis [11]. In our previous muscle MRI study of 12 patients, we found that four patients presented with severe thigh muscle fatty infiltration of posterior group and muscle fatty infiltration was one factor for refractory disease [12]. However, the proportion of patients with refractory ANM-SRP and pathological indicators associated with response to conventional immunosuppression are lacking due to few systematic follow-up studies. In this study, we therefore sought to evaluate the clinical and pathological factors influencing the therapeutic effect of conventional immunosuppression in a large cohort of Chinese patients with ANM-SRP.

Methods

Patient registry

This was a single-center, retrospective, observational cohort study including 48 Chinese patients who were diagnosed with ANM-SRP according to clinical, serological, and pathological criteria. Demographic data, clinical features, and initial drug treatment information were collected ([Supplementary Materials](#)). Written informed consent was obtained from all patients (or an appropriate family member where the patient was unable to provide consent). The procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation and approved by the Institutional Review Board.

Serum myositis antibody test

An immunoblot kit was used to determine the serum antibodies to SRP by detecting the 54kD subunit. The membrane strips were pretreated, incubated with patient serum, and subjected to enzyme binding. The results were scanned using EUROlineScan software, and were recorded as negative, weak positive (+), positive (++), and strong positive (+++). All the patients recruited were strong positive (+++).

Muscle MRI

Thirty-six patients underwent bilateral thigh MRI (tMRI) (3.0 T, GE 1.5 Sigma Twin Speed; GE Healthcare, Waukesha, WI, USA). Axial T1-weighted MRIs were used to evaluate the degree of fatty infiltration according to the modified Mercuri scale (0–5 scale; from normal appearance to complete fatty infiltration). Axial short T1 inversion recovery sequences were used to assess the degree of edema (0–5 scale, from normal to moderate intr fascicular global edema) [11]. Edema and fatty infiltration scores were calculated in the gluteus maximus at the pelvic level and thigh muscles (vastus intermedius, vastus medialis, vastus lateralis, rectus femoris, biceps femoris, semitendinosus, semimembranosus, adductor

magnus, sartorius, long adductor, and gracilis) at the mid-thighs. Additionally, we compared the thigh MRI of 36 patients with 36 controls (autoimmune necrotizing myopathy patients with negative anti-SRP antibody) to observe the damage in the tMRI. Total edema and the degree of fatty infiltration were compared before and after treatment as an indicator of therapeutic effect.

Muscle pathology

Muscle biopsies were taken from the biceps brachii or quadriceps femoris of all patients. Serial frozen sections were stained with hematoxylin and eosin (HE), modified Gomori trichrome, periodic acid-Schiff, oil red O, adenosinetriphosphate (ATP) enzyme (pH 4.5 and 10.8), NADH-tetrazolium reductase, succinate dehydrogenase (SDH), and cytochrome C oxidase (COX) stains. The sections were immunohistochemically stained with primary antibodies against human CD3, CD4, CD8, CD20, CD68, major histocompatibility complex class-I (MHC-I), membrane attack complex (MAC), dystrophin, sarco-glycans, and dysferlin.

BAFF and BAFF-R measurement

To further clarify the role of B lymphocytes in the therapeutic effect on ANM-SRP, immunohistochemical staining of B cell activating factor (BAFF), B cell activating factor receptor (BAFF-R) and CD19 was performed in 29 patients. The positive cellular expression of BAFF, BAFF-R and CD19-positive cells (numbers of positive cells / numbers of muscle fibers) was calculated per high-power microscopic field: 10 high-power microscopic fields (400×) were randomly selected from each section and the numbers of staining-positive cells and muscle fibers were counted under each high-power microscopic field (those with more than ½ area were included and those with less than ½ area were omitted). The average value of 10 high-power fields was calculated. Correlation of the positive cellular expression of BAFF, BAFF-R, CD19-positive cells was analyzed.

Additionally, muscle tissues of 14 patients with ANM-SRP and four healthy controls were sampled for semi-quantitative analysis of BAFF and BAFF-R. Radioimmunoprecipitation assay (RIPA) lysate (including protease inhibitor and phosphatase inhibitor) was added to the tissue samples for homogenization and the protein was extracted after lysis on ice for 30 min. An equal amount of protein (80 µg) was suspended in loading buffer, denatured at 100 °C for 5 min, and loaded on an SDS-PAGE gel. After being electrophoresed in 10% polyacrylamide gel, transferred electrophoretically to nitrocellulose membrane, the membrane was blocked with non-fat milk buffer for 1 h and then incubated with the primary antibodies overnight at 4 °C. The primary antibodies

were IgG-specific for BAFF (Abcam, ab16081, 1:500), BAFF-R (Abcam, ab5965, 1:500), and actin (Abcam, ab8226, 1:3000). After three 5-min washes (20-mmol/L Tris, pH 7.6, 8 g sodium chloride, 0.05% Tween-20), blots were incubated for 50 min with horseradish peroxidase-conjugated goat anti-rabbit IgG or rabbit anti-rat IgG (1:5000). After washing, bound IgG was detected auto-radiographically by enhanced chemiluminescence (Quantity One v.4.6.2).

Clinical follow-up and efficacy evaluation

The modified Rankin Scale score (mRS) was evaluated at 3, 6, and 12 months after treatment to evaluate the therapeutic effect on the basis of glucocorticoid therapy combined with other immunosuppressive agents or intravenous immunoglobulins (IVIg) in the study period. Patients were divided into non-refractory and refractory groups. If patients' muscle strengths returned to normal or was close to normal, the mRS scores were 0–2 points and those patients were placed in the non-refractory group. If there was still obvious limb weakness after 12 months of immunotherapy, the mRS scores were 3–5 points, or patients had a relapse, then the patients were placed into the refractory group [8, 13]. The relapse criteria were that the serum creatine kinase (CK) returned to above the patient's baseline level, rose to more than three times the reference upper limit, and limb weakness worsened again (excluding other causes such as exercise, electrolyte disturbance, thyroid dysfunction, or drug induction) [9].

Twenty-five patients with ANM-SRP were followed up by tMRI. We monitored the muscle fatty infiltration and edema changes by tMRI for 3, 6, 12, 18, and 24 months after treatment. Imaging indicators were the average change rates of thigh muscle fatty infiltration and edema (the scale gap of tMRI / interval time between before and after treatment) for 3, 6, 12, 18, and 24 months after treatment.

Statistical analysis

All analyses were performed using SPSS 17.0 software. Single factor and binary logistic regression analyses were used to compare the clinical, tMRI changes and pathological features between the two groups. The Mann–Whitney *U* test or Kruskal–Wallis test was used for the continuous variables and Chi-square test for categorical variables. Multivariate logistic regression analysis was performed on related predictors for refractory disease. Explanatory variables were selected using a liberal criterion ($p < 0.10$) for inclusion in the multivariate regression model. For all statistical analyses, significance was accepted as $p < 0.05$.

Results

The follow-up study was completed in 40 out of 48 enrolled patients, with a loss-to-follow-up rate of 16.67%. The mean follow-up duration was 3.85 ± 2.49 years (12 months to 9 years). After 12 months of treatment, 27 patients (67.5%) had normal or nearly normal muscle strength and an mRS 0–2 (the non-refractory group) and 13 patients (32.5%) still had muscle weakness and an mRS 3–5 (the refractory group).

Clinical refractory related factors: male, severe muscle weakness, concurrent ILD

In our cohort, the ratio of male to female participants was 14:34 and the cohort comprised 6 teenagers and 42 adults. The mean onset age was 40.9 ± 17.2 years old and the time to admission was 6 (4, 18) months. The numbers of patients with acute, subacute, and chronic disease were 5, 24, and 19, respectively. According to the Medical Research Council (MRC) classification, 18 patients (37.5%) had severe weakness (MRC 1–2/5), 20 patients (41.7%) moderate weakness (MRC 3/5), and 10 patients (20.8%) mild weakness (MRC 4–5/5). The severe weakness appeared in the lower limbs of 24 patients (50.0%), in the upper limbs of 6 patients (12.5%), and in all limbs of 18 patients (37.5%). Additional clinical baseline data can be seen in the [Supplementary Material](#).

The mean onset age in the non-refractory group and refractory group were 37.26 ± 18.06 and 50.77 ± 15.77 years old, respectively ($P = 0.029$). The proportions of weight lost after the onset of disease were 40.7% in the non-refractory group and 76.9% in the refractory group ($P = 0.032$). Furthermore, the percentage of ILD was 22.2% in the non-refractory group and 69.2% in the refractory group ($P = 0.004$) and the proportion of patients initially treated with methotrexate was 59.3% for the non-refractory group and 23.1% for the refractory group ($P = 0.032$; Table 1). Binary logistic regression analysis verified that the risk factors for refractory patients were being male (OR = 19.57, 95%CI = 1.49–256.53), severe muscle weakness (OR = 7.51, 95%CI = 41.03–54.88), and the presence of ILD (OR = 39.70, 95%CI = 3.04–518.38; Table 2).

Imaging refractory-related factors: quick development of muscle fatty infiltration

Thirty-six patients underwent tMRI, which showed fatty infiltration in 29 patients (80.6%) and edema in 32 patients (88.9%). The fatty infiltration and edema mainly affected the gluteus maximus, adductor magnus, semimembranosus, semitendinosus and the long head of the biceps both in the refractory and non-refractory groups. There was no statistically significant difference between the thigh MRI of patients with ANM-SRP and 36 ANM patients with negative anti-SRP antibody.

Table 1 Clinical indicators between refractory and non-refractory group

	Non-refractory group (27)		Refractory group (13)		P
	Total(n)	Proportion(%)	Total(n)	Proportion(%)	
Clinical syndromes					
Gender(male: female)	5:22	18.5	6:7	46.2	0.067
Cervical flexion weakness	22	81.5	11	84.6	0.807
Severe myasthenia	9	33.3	8	61.5	0.091
Dysphagia	9	33.3	5	38.5	0.750
Dysmasesia	7	25.9	1	7.7	0.177
Myalgia	10	37.0	4	30.8	0.697
Amyotrophy	11	40.7	6	46.2	0.746
Weight lost	11	40.7	10	76.9	0.032
Auxiliary examination					
ILD	6	22.2	9	69.2	0.004
Elevated ESR	5	18.5	5	38.5	0.872
Elevated ANA	12	44.4	8	61.5	0.311
Combined with anti-Ro-52 antibody	7	25.9	5	38.5	0.418
Initial therapy					
GC	3	11.1	4	30.8	0.132
GC + IVIg+MTX	10	37.0	3	23.1	0.390
GC + MTX	6	22.2	1	7.7	0.269
GC + IVIg	5	18.5	3	23.1	0.744
GC + OI	4	14.8	5	38.5	0.098
OI + MTX	16	59.3	3	23.1	0.032
OI + IVIg	15	55.6	6	46.2	0.588

ILD Interstitial lung disease, GC Glucocorticoid, MTX Methotrexate, IVIg Intravenous immunoglobulin, OI Other immunosuppressant

Thigh MRI follow-up showed an increasing rate of fatty infiltration at 3, 6, 12, 18, and 24 months with 3.44, 1.45, 0.68, 0.41, and 0.11, respectively (Fig. 1). The reducing rate of edema at 3, 6, 12, 18, and 24 months was 2.37, 2.72, 1.07, 0.55, and 0.57, respectively. The mean fatty infiltration rate of the thigh muscles at 3 months was higher in the refractory group than in the non-refractory group ($P = 0.022$). However, there was no statistically significant difference between the two groups in the increasing rate of fatty infiltration and the reducing rate of edema at the remaining periods (Table 3).

Table 2 Binary logistic analysis of clinical indicators between refractory and non-refractory group

Indicator	OR	95%CI	P
Gender(male)	19.57	1.49–256.53	0.024*
Severe muscle weakness	7.51	41.03–54.88	0.047*
With ILD	39.70	3.04–518.38	0.005*

ILD Interstitial lung disease
* $P < 0.05$

Pathological refractory-related factors: high expression of BAFF and BAFF-R in muscle

Muscle biopsies revealed a large variation in fiber size in all patients except two patients with terminal changes. Muscle fiber hypertrophy appeared in 10 patients (22.7%). Muscle fiber necrosis with myophagocytosis appeared in 40 patients (90.9%) and muscle fiber regeneration appeared in 43 patients (97.7%). CD68⁺ macrophages appeared in necrotic fibers in the perimysium in 41 patients (93.2%). Ragged blue fibers were found in three patients using SDH staining (7.5%), and COX-negative muscle fibers were found in six patients using Cox staining (15%). Mild-to-moderate connective tissue proliferation appeared in 13 patients (29.5%). Perivascular lymphocyte infiltration in the perimysium was observed in nine patients (20.5%), while CD3⁺, CD4⁺ and CD8⁺ lymphocytes appeared in 22 (50%), 26 (59.1%) and 23 (52.3%) patients, respectively. CD20⁺ lymphocytes appeared in four patients (9.1%) and CD19⁺ lymphocytes appeared in 21 patients (72.4%) of 29 tested patients. MAC deposition in muscle fibers was seen in 32 of 37 patients (86.5%). MHC-I positive myofibrils appeared in 37 of 40 patients (92.5%; Fig. 2).

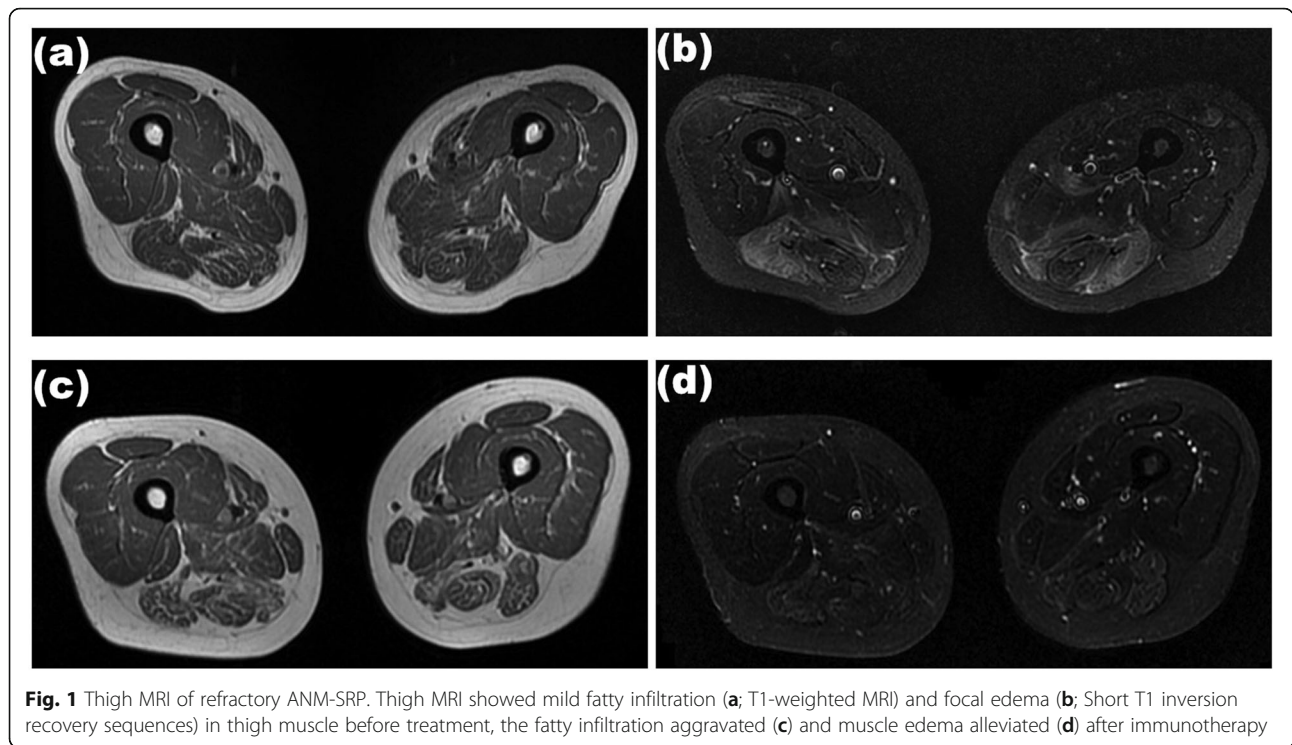


Fig. 1 Thigh MRI of refractory ANM-SRP. Thigh MRI showed mild fatty infiltration (**a**; T1-weighted MRI) and focal edema (**b**; Short T1 inversion recovery sequences) in thigh muscle before treatment, the fatty infiltration aggravated (**c**) and muscle edema alleviated (**d**) after immunotherapy

Pathological indicators like muscle fiber necrosis, regeneration, atrophy, hypertrophy, connective tissue proliferation, infiltration of CD3⁺, CD4⁺, CD8⁺, and CD20⁺ lymphocytes, infiltration of CD68⁺ macrophages, MAC deposition, and MHC-I positive expression were not significantly different between the refractory and non-refractory groups.

BAFF staining revealed that 10 of 29 patients (34.5%) with positive deposition in necrotic tissue regenerated muscle fibers and individual lymphocytes (Fig. 3). Positive BAFF-R expression was found in 24 of 29 patients (82.8%), mainly expressed in necrotic muscle fibers,

muscle perimysium, muscle underwear and by lymphocytes infiltrating around blood vessels (Fig. 4). The expression level of CD19⁺ lymphocytes overlapped with BAFF-R (Fig. 5). Spearman correlation tests showed a correlation between BAFF-R and CD19 ($R = 0.818$, $P < 0.001$).

The positive cellular expression of BAFF-R in muscles was 0.27 ± 0.14 for the non-refractory group and 0.42 ± 0.23 for the refractory group ($P = 0.036$). The positive cellular expression of CD19 in skeletal muscle was 0.18 ± 0.08 for the non-refractory group and 0.36 ± 0.21 for the refractory group ($P = 0.002$). There was no

Table 3 Imaging indicators between refractory and non-refractory group

tMRI	Average change rates	Non-refractory group (16)	Refractory group (9)	P
Fatty infiltration	3 months	2.64	5.55	0.022*
	6 months	1.37	1.60	0.118
	12 months	0.77	0.59	0.305
	18 months	0.43	0.38	0.534
	24 months	0.14	0.17	0.176
Edema	3 months	3.69	2.17	0.240
	6 months	2.80	2.56	0.206
	12 months	1.18	1.17	0.627
	18 months	0.99	0.70	0.431
	24 months	0.64	0.60	0.386

tMRI Thigh MRI
*P<0.05

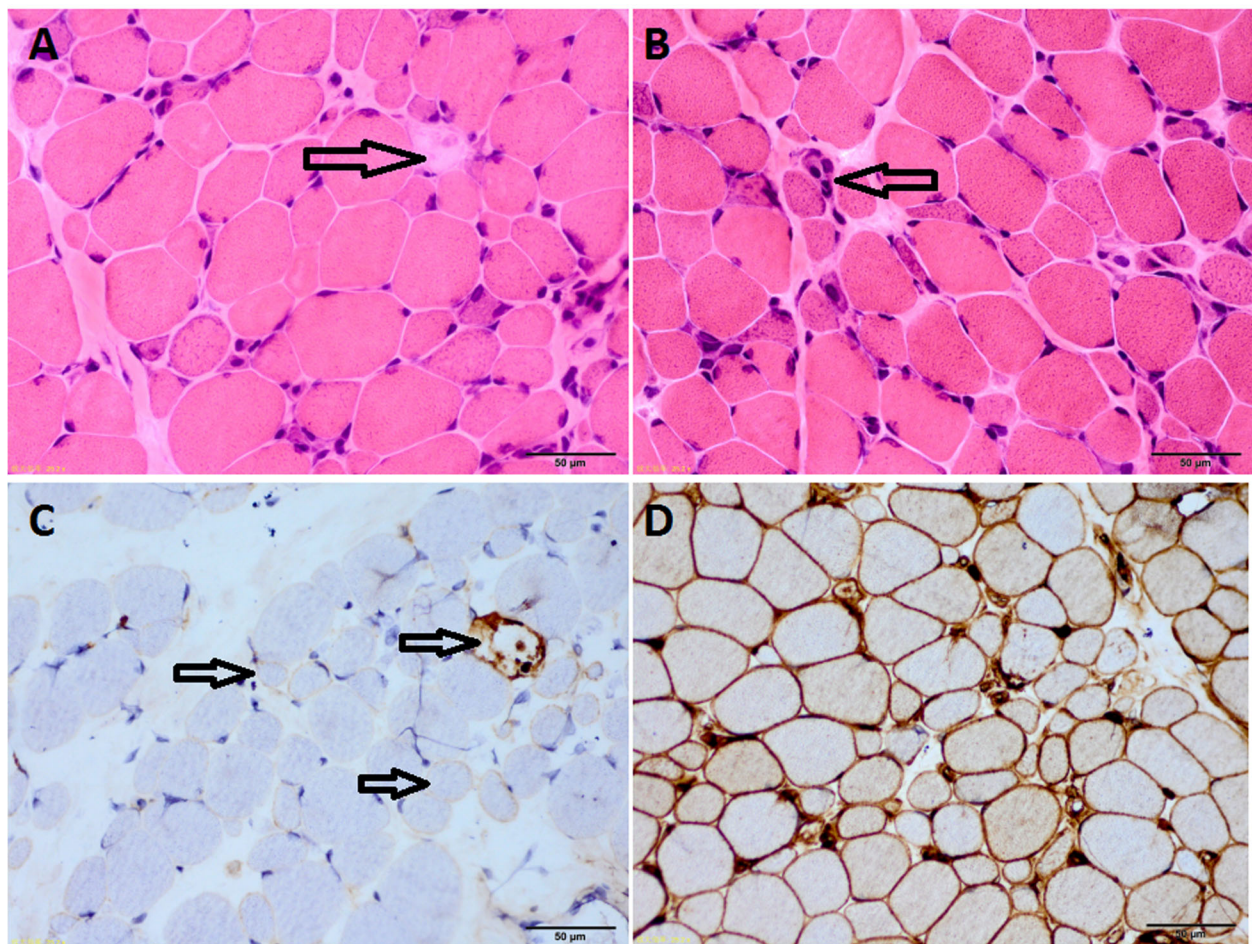


Fig. 2 Muscle pathology of ANM-SRP ($\times 400$). Muscle fibers show necrosis (a, arrow) and regeneration (b, arrow), with little inflammatory cell infiltration (H&E staining); MAC staining (c) showed MAC deposition of necrotic muscle fiber and non-necrotic sarcolemma (arrow) and MHC-I staining (d) showed positive expression of sarcolemma and partial cytoplasm, accompanied by decreased capillaries

statistically significant difference in the expression of BAFF (Table 4). The western blots of BAFF and BAFF-R in skeletal muscle of patients and healthy controls also showed that BAFF-R expression in patients' skeletal muscle was significantly higher than that of the healthy controls. BAFF was expressed in skeletal muscle of both patients and healthy controls (Fig. 6).

Discussion

This study examined the factors contributing to poor response to immunosuppressive agents in ANM-SRP patients. We found that male patients with ANM-SRP have a poorer prognosis, but this conclusion may still need to be confirmed in a larger sample. Our previous study followed up three child patients with good prognosis, all of whom were female [14], while most studies had not found a correlation between gender and refractory disease [8, 13]. We also found that severe muscle

weakness before the initiation therapy indicated a poor response which has also been reported by Aggarwal and colleagues in a cohort of 25 patients with ANM-SRP [15]. More than 90% of patients in a Brazilian study showed mild and moderate muscle weakness, and the refractory rate was 42.9% [16]. Whether there is a racial difference between the degree of limb weakness and the therapeutic effect needs further analysis. In the refractory group, the proportion of patients with ILDs was high (34.8%) and its incidence was close to that of Brazilian patients (36%) [16], which is higher than the 25% reported in Japan, Europe and America [8, 17, 18]. The combination of ILDs is an important factor affecting patients' quality of life and prognosis, while the use of mycophenolate or tacrolimus may improve the therapeutic effect in patients with the combination of ILDs [18, 19].

Our study added skeletal muscle MRI to monitor disease activity and severity and was used for long-term

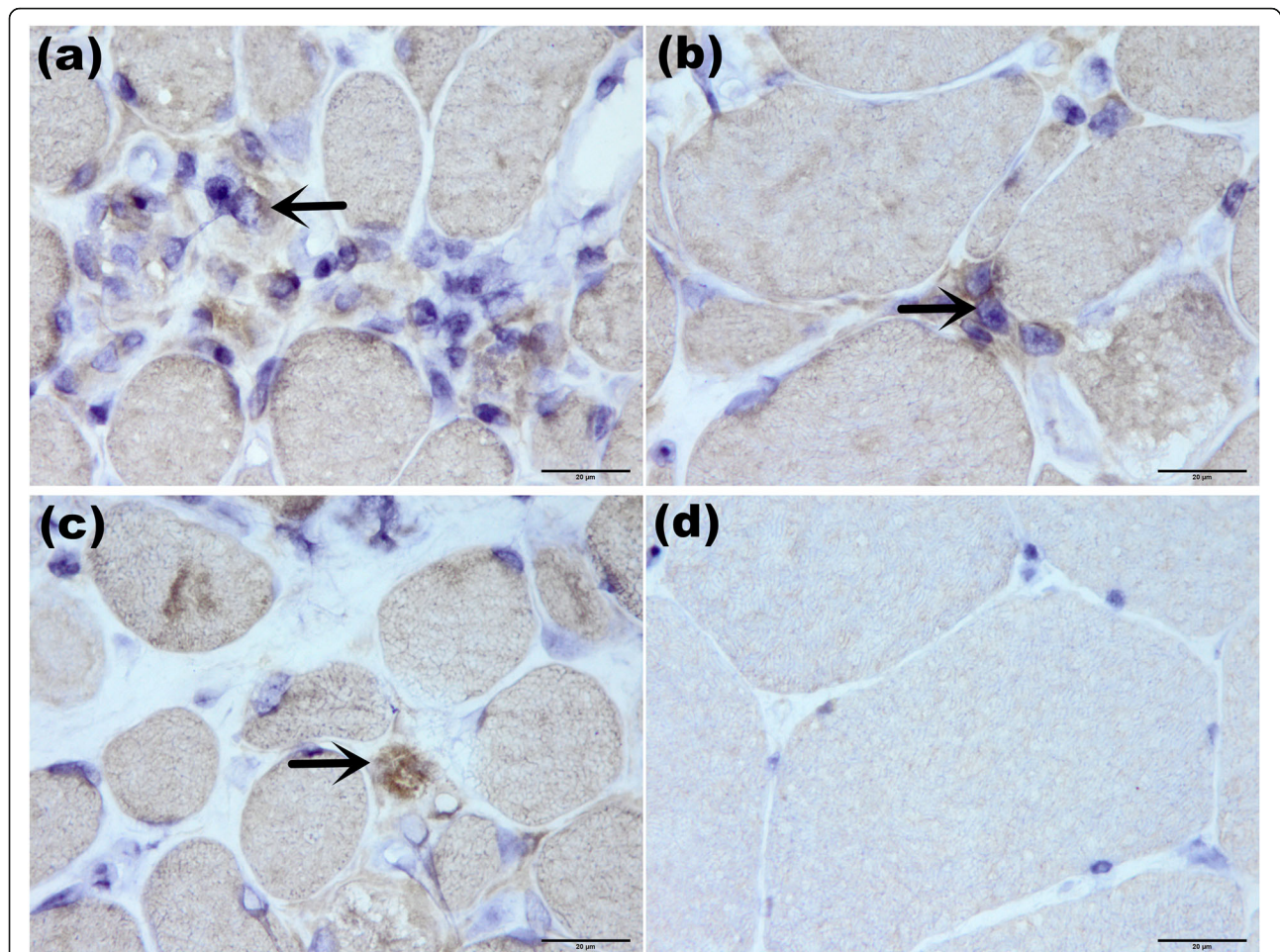


Fig. 3 BAFF staining of ANM-SRP($\times 1000$). BAFF was positively expressed on the surface of inflammatory cells in endomysium (**a, b**, arrow) and on the surface of inflammatory cells invading necrotic muscle fibers (**c**, arrow). No BAFF positive expression was found in healthy control (**d**)

follow-up of patients. The fatty infiltration exacerbation of skeletal muscle MRI in the early treatment period often suggests a refractory disease. Similar conclusions can be seen in other MRI studies of skeletal muscle in idiopathic inflammatory myopathy [20]. A previous study showed that muscle fatty infiltration may be closely related to the prognosis of ANM-SRP and is often a marker of glucocorticoid resistance or refractory treatment [12, 21]. Therefore, it is recommended that patients with ANM-SRP should have skeletal muscle MRIs within 3 to 6 months after treatment initiation to monitor the efficacy of immunotherapy and the progression of the disease. For patients with early fatty infiltration changes, immunotherapy should be strengthened and more frequent follow-up should be conducted. Whether the approach preventing fatty infiltration of skeletal muscle will reduce the poor response to treatment warrants further studies.

In this study, we observed that BAFF-R expression was upregulated in the muscle of patients with ANM-SRP. BAFF, a member of the tumor necrosis factor (TNF) ligand family, has been shown to play an important role in the homeostasis and autoimmunity of B lymphocytes [22]. BAFF-R is expressed in B lymphocytes and binds with high specificity to BAFF. BAFF-BAFFR interaction plays a leading role in maintaining peripheral mature and immature B lymphocyte pool and is the main receptor required for BAFF-mediated survival of mature B lymphocytes [23]. Previous studies have detected the upregulation of BAFF and BAFF-R in the serum or muscle of dermatomyositis, polymyositis, and anti-synthase antibody syndrome patients [24, 25], and its level correlated with the activity of idiopathic inflammatory myopathy [24]. Patients with ANM-SRP had high BAFF-R and CD19 expression, and the refractory patients had significantly higher BAFF-R and CD19 expression than non-

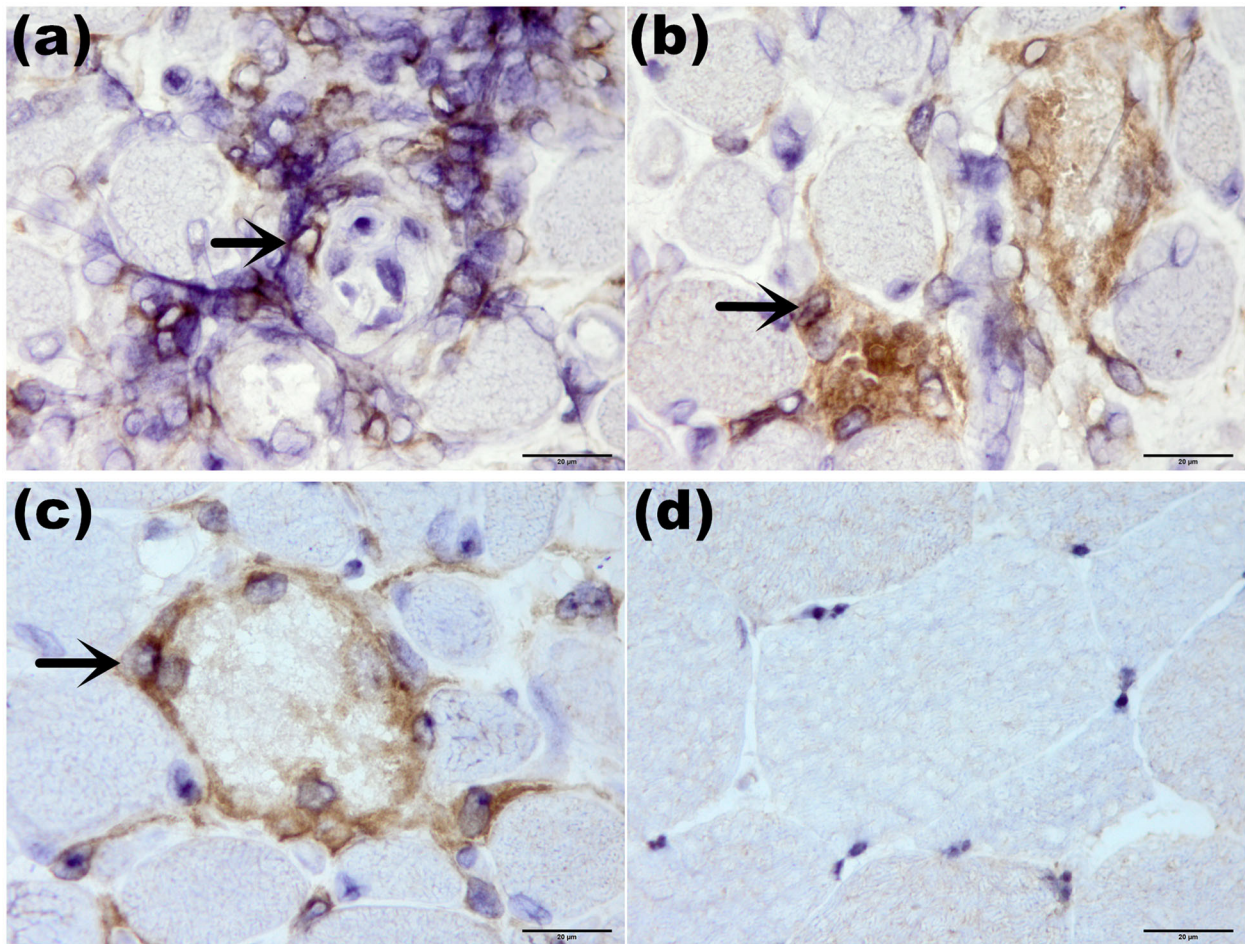


Fig. 4 BAFF-R staining of ANM-SRP($\times 1000$). BAFF-R was positively expressed on the surface of inflammatory cells surrounding muscle fibers (**a**, arrow) or on the surface of inflammatory cells surrounding and invading necrotic muscle fibers (**b, c**, arrow). No BAFF-R positive expression was found in healthy controls (**d**)

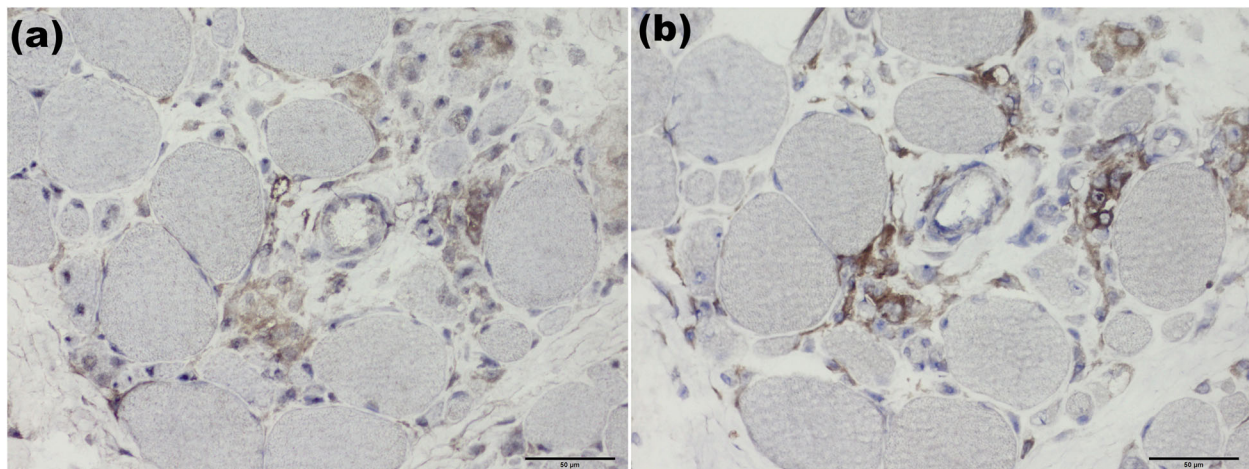


Fig. 5 The expression sites of BAFF-R (**a**, $\times 400$) were highly overlapping compared with CD19 (**b**, $\times 400$)

Table 4 Pathology indicators between refractory and non-refractory group

Positive cellular expression	Non-refractory group(19 cases)	Refractory group(10 cases)	P
BAFF	0.06 ± 0.03	0.06 ± 0.05	0.542
BAFF-R	0.27 ± 0.14	0.42 ± 0.23	0.036*
CD19	0.18 ± 0.08	0.36 ± 0.21	0.002*

*P<0.05

refractory patients, which suggests that BAFF and its receptors may cause muscle fiber injury and lymphocyte proliferation. CD19 and BAFF-R expression in skeletal muscle might be effective pathological indicators to predict the treatment effects in patients. A number of small sample studies suggest that removal of B cells is effective for treating refractory ANM-SRP [26], while this study also provided pathological evidence for the use of B lymphocyte depletion drugs and suggested that BAFF inhibitors [27] may be effective in the treatment of patients with ANM-SRP.

Our study has several limitations that require comment. First, it was a single-center and hospital-based study that focused on urban patients only and therefore could not reveal the true situation of patients with ANM-SRP in rural areas or remote regions. Patients who did not seek treatment or who died before arriving

at the hospital were not included in the study. Furthermore, it was a retrospective, observational cohort study, with initial differences in therapy in some patients, which may have affected the results, so we used a multivariate logistic regression analysis to reduce this interference. Prospective studies with a larger sample are needed in the future to verify our conclusions.

Conclusion

The present study examined a multitude of clinical and pathological factors that may be associated with the refractory ANM-SRP. We found that BAFF-R expression in skeletal muscle of ANM-SRP was upregulated. Being male, severe muscle weakness, concurrent ILD, quick development of muscle fatty infiltration, and higher BAFF-R and B lymphocyte muscle infiltration may be the factors associated with refractory ANM-SRP.

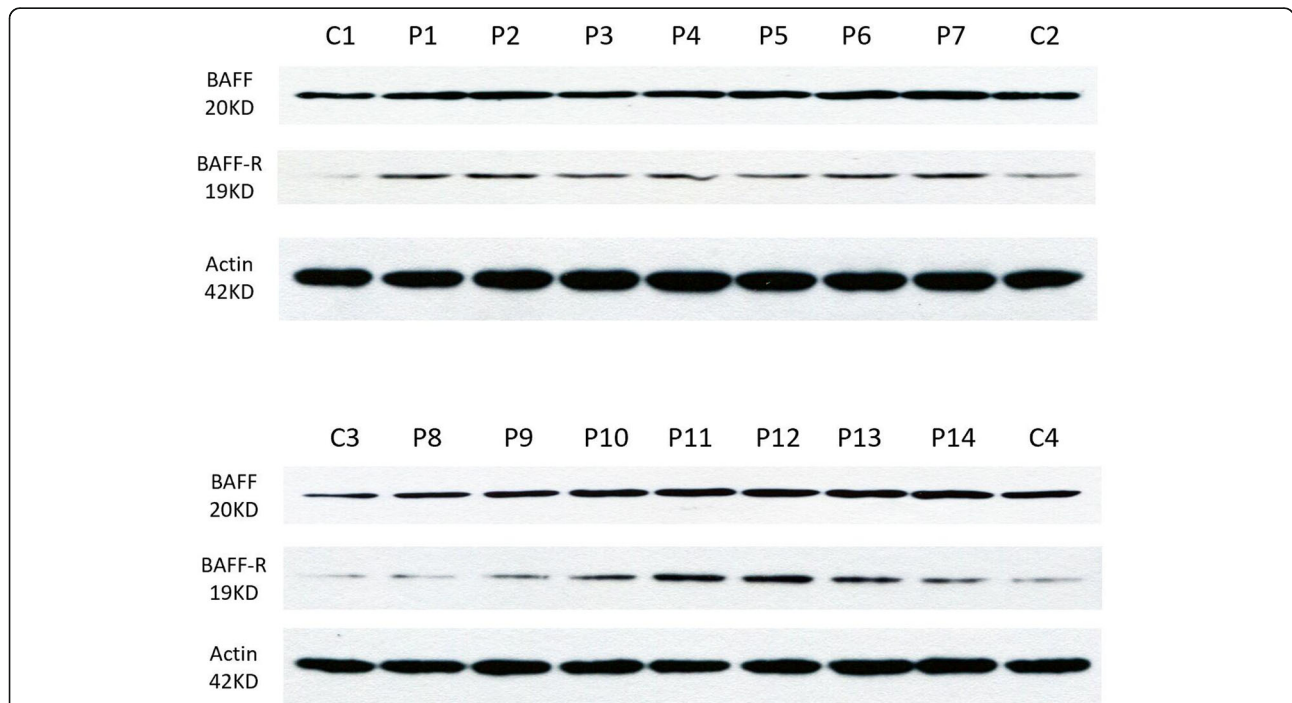


Fig. 6 Western bolt of BAFF and BAFF-R in skeletal muscle of ANM-SRP. The results showed that the expression of BAFF-R in skeletal muscle of the patients was significantly higher than that of the healthy control. BAFF were expressed in skeletal muscle of both patients and healthy control

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13023-020-01431-7>.

Additional file 1: Supplementary materials. Demographic and clinical features of patients with ANM-SRP.

Abbreviations

ANM-SRP: Autoimmune necrotizing myopathy with anti-signal recognition particle antibodies; BAFF: B cell activating factor; BAFF-R: B cell activating factor receptor; CK: Creatine kinase; ILD: Interstitial lung disease; MRI: thigh MRI; HE: Hematoxylin and eosin; ATP: Adenosinetriphosphate; SDH: Succinate dehydrogenase; COX: Cytochrome C oxidase; MHC-I: Major histocompatibility complex class -I; MAC: Membrane attack complex; IVIg: Intravenous immunoglobulins; mRS: The modified Rankin Scale score; MRC: Medical Research Council

Acknowledgments

We thank YuehuanZuo and Jing Liu for their technical help in pathology, and thank Hongjun Hao for their technical help in the myositis antibody test. We also thank the patients and their families for their participation in this project. We thank Dr. Alla Bradley from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing a draft of this manuscript.

Authors' contributions

All authors were involved in drafting the article and in revising it critically for intellectual content. Yun Yuan conceived and designed the study. Yawen Zhao analyzed the data, wrote the first version of the manuscript. Yawen Zhao and Yilin Liu evaluated the muscle MRI images. Wei Zhang, Zhaoxia Wang and Yun Yuan revised the manuscript. The author(s) read and approved the final manuscript.

Funding

This work was supported by the National Nature Science Foundation of China (grant numbers 81571219) and Beijing Municipal Science and Technology Commission (grant numbers Z151100003915126).

Availability of data and materials

The patients data used in this study are included in this publish article and its supplementary files.

Ethics approval and consent to participate

The study was performed in accordance with the ethical standards of the responsible committees on human experimentation and approved by the Institutional Review Board (no. 2011[419]). Informed consent for all examinations was obtained from the patients or their guardians. The protocol in the study strictly followed the rules of the Declaration of Helsinki.

Consent for publication

Applicable.

Competing interests

The authors declare no conflicts of interest.

Received: 17 February 2020 Accepted: 28 May 2020

Published online: 08 July 2020

References

- Miller T, Al-Lozi MT, Lopate G, Pestronk A. Myopathy with antibodies to the signal recognition particle: clinical and pathological features. *J Neurol Neurosurg Psychiatry*. 2002;73:420–8. <https://doi.org/10.1136/jnnp.73.4.420>.
- Pinal-Fernandez I, Parks C, Werner JL, Albayda J, Paik J, Danoff SK, et al. Longitudinal course of disease in a large cohort of myositis patients with autoantibodies recognizing the signal recognition particle. *Arthritis Care Res (Hoboken)*. 2017;69:263–70. <https://doi.org/10.1002/acr.22920>.
- Ashton C, Junckerstorff R, Bundell C, Hollingsworth P, Needham M. Treatment and outcomes in necrotising autoimmune myopathy: an Australian perspective. *Neuromuscul Disord*. 2016;26:734–40. <https://doi.org/10.1016/j.nmd.2016.08.013>.
- Gómez GN, Gargiulo ML, Pérez N, Collado MV, Suárez LV, Khoury M, et al. Autoantibodies in adult patients with idiopathic inflammatory myopathies in Buenos Aires. *Medicina (B Aires)*. 2016;76:129–34.
- Vincze M, Molnár PA, Tumpek J, Szollosi L, Gyetvai A, Kapitány A, et al. An unusual association: anti-Jo1 and anti-SRP antibodies in the serum of a patient with polymyositis. *Clin Rheumatol*. 2010;29:811–4. <https://doi.org/10.1007/s10067-010-1394-6>.
- O'Grady J, Harty L, Mayer N, Critcher V, Ryan J. Immune-mediated necrotizing myopathy, associated with antibodies to signal recognition particle, together with lupus nephritis: case presentation and management. *J Clin Med Res*. 2015;7:490–4.
- Binns EL, Moraitis E, Maillard S, Tansley S, McHugh N, Jacques TS, et al. Effective induction therapy for anti-SRP associated myositis in childhood: A small case series and review of the literature. *Pediatr Rheumatol Online J*. 2017;15:77. <https://doi.org/10.1186/s12969-017-0205-x>.
- Suzuki S, Nishikawa A, Kuwana M, Nishimura H, Watanabe Y, Nakahara J, et al. Inflammatory myopathy with anti-signal recognition particle antibodies: case series of 100 patients. *Orphanet J Rare Dis*. 2015;10:61. <https://doi.org/10.1186/s13023-015-0277-y>.
- Valiyil R, Casciola-Rosen L, Hong G, Mammen A, Christopher-Stine L. Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. *Arthritis Care Res (Hoboken)*. 2010;62:1328–34. <https://doi.org/10.1002/acr.20219>.
- Arlet JB, Dimitri D, Pagnoux C, Boyer O, Maisonobe T, Authier FJ, et al. Marked efficacy of a therapeutic strategy associating prednisone and plasma exchange followed by rituximab in two patients with refractory myopathy associated with antibodies to the signal recognition particle (SRP). *Neuromuscul Disord*. 2006;16:334–6. <https://doi.org/10.1016/j.nmd.2006.03.002>.
- Ikeda K, Mori-Yoshimura M, Yamamoto T, Sonoo M, Suzuki S, Kondo Y, et al. Chronic myopathy associated with anti-signal recognition particle antibodies can be misdiagnosed as facioscapulohumeral muscular dystrophy. *J Clin Neuromuscul Dis*. 2016;17:197–206.
- Zheng Y, Liu L, Wang L, Xiao J, Wang Z, Lv H, et al. Magnetic resonance imaging changes of thigh muscles in myopathy with antibodies to signal recognition particle. *Rheumatology (Oxford)*. 2015;54:1017–24. <https://doi.org/10.1093/rheumatology/keu422>.
- Kassardjian CD, Lennon VA, Alfugham NB, Mahler M, Milone M. Clinical features and treatment outcomes of necrotizing autoimmune myopathy. *JAMA Neurol*. 2015;72:996–1003. <https://doi.org/10.1001/jamaneurol.2015.1207>.
- Zhao Y, Liu X, Zhang W, Yuan Y. Childhood autoimmune necrotizing myopathy with anti-signal recognition particle antibodies. *Muscle Nerve*. 2017;56:1181–7. <https://doi.org/10.1002/mus.25575>.
- Aggarwal R, Bandos A, Reed AM, Ascherman DP, Barohn RJ, Feldman BM, et al. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis. *Arthritis Rheumatol*. 2014;66:740–9. <https://doi.org/10.1002/art.38270>.
- De Souza FHC, Miossi R, Shinjo SK. Necrotising myopathy associated with anti-signal recognition particle (anti-SRP) antibody. *Clin Exp Rheumatol*. 2017;35:766–71.
- Christopher-Stine L, Casciola-Rosen LA, Hong G, Chung T, Corse AM, Mammen AL. A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. *Arthritis Rheum*. 2010;62:2757–66. <https://doi.org/10.1002/art.27572>.
- Mira-Avendano IC, Parambil JG, Yadav R, Arrossi V, Xu M, Chapman JT, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. *Respir Med*. 2013;107:890–6. <https://doi.org/10.1016/j.rmed.2013.02.015>.
- Kurita T, Yasuda S, Oba K, Odani T, Kono M, Otomo K, et al. The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. *Rheumatology (Oxford)*. 2015;54:1536. <https://doi.org/10.1093/rheumatology/kev192>.
- Day J, Patel S, Limaye V. The role of magnetic resonance imaging techniques in evaluation and management of the idiopathic inflammatory myopathies. *Semin Arthritis Rheum*. 2017;46:642–9. <https://doi.org/10.1016/j.semarthrit.2016.11.001>.
- Yao L, Yip AL, Shrader JA, Mesdaghinia S, Volochayev R, Jansen AV, et al. Magnetic resonance measurement of muscle T2, fat-corrected T2 and fat fraction in the assessment of idiopathic inflammatory myopathies. *Rheumatology (Oxford)*. 2016;55:441–9. <https://doi.org/10.1093/rheumatology/kev344>.

22. Shulga-Morskaya S, Dobles M, Walsh ME, Ng LG, MacKay F, Rao SP, et al. B cell-activating factor belonging to the TNF family acts through separate receptors to support B cell survival and T cell-independent antibody formation. *J Immunol*. 2004;173:2331–41. <https://doi.org/10.4049/jimmunol.173.4.2331>.
23. Thompson JS, Bixler SA, Qian F, Vora K, Scott ML, Cachero TG, et al. BAFF-R, a newly identified TNF receptor that specifically interacts with BAFF. *Science*. 2001;293(5537):2108–11. <https://doi.org/10.1126/science.1061965>.
24. López De Padilla CM, McNallan KT, Crowson CS, Bilgic H, Bram RJ, Hein MS, et al. BAFF expression correlates with idiopathic inflammatory myopathy disease activity measures and autoantibodies. *J Rheumatol*. 2013;40:294–302. <https://doi.org/10.3899/jrheum.120555>.
25. Kryštůfková O, Barbasso Helmers S, Venalis P, Malmström V, Lindroos E, Vencovský J, et al. Expression of BAFF receptors in muscle tissue of myositis patients with anti-Jo-1 or anti-Ro52/anti-Ro60 autoantibodies. *Arthritis Res Ther*. 2014;16:454. <https://doi.org/10.1186/s13075-014-0454-8>.
26. Aggarwal R, Oddis CV, Goudeau D, Koontz D, Qi Z, Reed AM, et al. Autoantibody levels in myositis patients correlate with clinical response during B cell depletion with rituximab. *Rheumatology (Oxford)*. 2016;55:991–9. <https://doi.org/10.1093/rheumatology/kew275>.
27. Liu Z, Davidson A. BAFF inhibition: a new class of drugs for the treatment of autoimmunity. *Exp Cell Res*. 2011;317:1270–7. <https://doi.org/10.1016/j.yexcr.2011.02.005>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

