Neurology Asia 2021; 26(2) : 291 – 299

Immune-mediated necrotizing myopathy in a multi-ethnic Malaysian cohort

[1]Cheng-Yin Tan, [1,3]Tomica Ambang, [2]Jasmin Raja, [1]Nortina Shahrizaila, [2]Sargunan Sockalingam, [4]Shigeaki Suzuki, [5]Ichizo Nishino, [3]Kum-Thong Wong, [1]Khean-Jin Goh

Divisions of [1]Neurology and [2]Rheumatology, Department of Medicine, [3]Department of Pathology, University of Malaya, Kuala Lumpur, Malaysia. [4]Department of Neurology, Keio University School of Medicine, Tokyo; [5]Department of Neuromuscular Research, National Institute of Neuroscience, National Center for Neurology and Psychiatry, Tokyo, Japan

Abstract

Objective: To describe the clinical features and treatment outcomes of immune-mediated necrotizing myopathy (IMNM) in Malaysian patients. *Methods:* We describe a cohort of IMNM patients from a tertiary medical centre in Kuala Lumpur, Malaysia, in terms of their demography, clinical features, investigations, treatments and outcome. Comparisons were made between the anti-signal recognition particle (SRP) positive, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) positive and seronegative subgroups.
Results: IMNM was seen in 23.7% of inflammatory myopathy cases in the University of Malaya muscle biopsy databank. Of these, 35 patients who underwent serological testing for IMNM myositis-specific antibodies were included in the study. 45.7% were anti-SRP positive, 20% anti-HMGCR positive, and 28.6% seronegative. Two (5.7%) patients had dual positivity. Mean age of onset was 37.1 ± 17.0 years (range of 8 to 76 years) with female predominance (74.3%). Twenty three (65.7%) patients presented subacutely (≤ 6 months) with the majority having symmetrical severe weakness (MRC grade ≤ 3), with proximal and lower limb predominance. Four (11.4%) had respiratory involvement but none had cardiac symptoms. Extramuscular manifestations included skin lesions (20%), arthralgia (5.7%), associated connective tissue disease (11.4%) and none with cancer. Anti-SRP positivity was significantly associated with muscle wasting and anti-HMGCR group with cutaneous involvement. Anti-HMGCR positivity was not significantly associated with statin use. Most patients required a combination of at least two immunotherapies and at follow up, 50% showed good recovery with minimal weakness while a third had at least moderately severe disability.
Conclusion: IMNM is a common inflammatory myopathy seen in all ethnic groups in Malaysia. Its clinical characteristics are consistent with other populations. Extramuscular involvement is uncommon. Most patients require combined immunosuppressive therapy with variable outcome; about half having a good outcome with minimal disability and a third with more severe disease with significant persistent disability.

Keywords: Immune-mediated necrotizing myopathy; necrotizing autoimmune myopathy; anti-SRP myopathy; anti-HMGCR myopathy; inflammatory myopathy; necrotizing myopathy

INTRODUCTION

Immune-mediated necrotizing myopathy (IMNM) is increasingly recognized as one of the more common subtypes of idiopathic inflammatory myopathy. Typically, IMNM presents subacutely with symmetrical proximal muscle weakness and markedly raised creatine kinase (CK).[1-3] The disorder is characterized pathologically by muscle necrosis and regenerating muscle fibers without prominent inflammatory cells.[3-6] Necrotizing myopathy has also been associated with other disorders viz. connective tissue disease, drug toxicity and viral infections apart from IMNM.[2,6] Two myositis-specific antibodies (MSA) have been discovered to be associated with IMNM viz. anti-signal recognition particle (SRP) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) autoantibodies.[1-3,6] Generally, IMNM has been regarded as

Address correspondence to: Khean-Jin Goh, Division of Neurology, Department of Medicine, Faculty of Medicine, University of Malaya, Lembah Pantai, 50603 Kuala Lumpur, Malaysia. Tel: +60379492891, Email: gohkj@ummc.edu.my

Date of Submission: 10 January 2021; Date of Acceptance: 12 January 2021

less responsive to corticosteroids than other inflammatory myopathies and often require a second immunosuppressant in addition to corticosteroids.[2,7-11] However, treatment strategies have not been evaluated in prospective trials apart from case series and expert opinions.

The aim of this study was to describe the clinical features, laboratory findings and treatment outcomes in a cohort of multi-ethnic Malaysian IMNM patients in whom myositis specific antibodies were tested and to evaluate differences between various subtypes viz. anti-SRP positive, anti-HMGCR positive and those who were seronegative.

METHODS

The University of Malaya Medical Centre (UMMC) is a major tertiary neuromuscular referral centre in Kuala Lumpur and the UMMC Department of Pathology muscle biopsy databank consists of cases who underwent muscle biopsy at UMMC as well as other hospitals, whose biopsies were then referred for diagnostic histopathology. Cases from the databank from its inception in 1995 to 2016 with a diagnosis of inflammatory myopathy were selected and their muscle biopsy slides were reviewed by an investigator trained by an experienced muscle pathologist (TA and KTW) and were re-classified according to the European Neuromuscular Centre (ENMC) clinico-pathological criteria or the ENMC inclusion body myositis diagnostic criteria.[12,13]

IMNM was diagnosed based on compatible clinical features, histopathological features of necrotizing myopathy, raised serum CK and one of the following laboratory findings viz. myopathic electromyography (EMG) changes, MRI changes suggestive of inflammatory myopathy or positive IMNM antibodies. For cases between 2012 and 2016, serological testing was carried out using the Euroimmun myositis profile 3 immunoblot assay, which measured the anti-SRP antibody. Other myositis antibodies tested by the assay included the anti-tRNA synthetases viz. Jo1, PL7, PL12, EJ, OJ as well as anti-Mi2, anti-Ro52, anti-Ku, anti-PM/Scl75, anti PM/Scl100 and anti-U1RNP. Samples negative for anti-SRP antibody using the immunoblot assay were then referred to Keio University for re-analyses of anti-SRP antibody by RNA immunoprecipitation and also for anti-HMGCR antibodies by enzyme-linked immunosorbent assay (ELISA) test.[8,10] Patients were divided into three different serological subgroups, seronegative, anti-SRP antibody positive or anti-HMGCR antibody positive.[3]

Clinical data was provided by the referring physician and included demographic data, history and neurologic findings, laboratory data, drug therapy and clinical response to treatment. Subacute onset was defined as duration of illness before presentation ≤ 6 months and chronic when > 6 months.[8] Severity of weakness was based on the Medical Research Council (MRC) grade of the weakest muscle group with severe weakness defined as MRC ≤ 3. An association with malignancy was defined as the presence of cancer within two years of the diagnosis of myopathy. Cardiac or respiratory involvement was confirmed to be present if there was clear documentation of symptoms with/without supportive evidence from standard investigations such as spirometry, high resolution computed tomography (HRCT) of the chest, and echocardiography. For laboratory data, C-reactive protein (CRP), an inflammatory marker, was raised if ≥ 1 mg/dL and anti-nuclear antibodies (ANA), when the titer ≥ 1:160. Neurological outcome was assessed using the modified Rankin Scale (mRS).[9,10] Patients who responded to treatment and returned to their jobs were defined as recovered (mRS = 0 or 1). Patients who responded partially and resumed most of the daily activities were defined as having a mild deficit (mRS = 2). Patients who responded minimally and required support in daily activities were defined as having a severe deficit (mRS = 3-5).

All patients provided informed consent for muscle biopsy and blood investigations. The study was approved by the University of Malaya Medical Research Ethics Committee (MECID 20146-293).

Statistical analysis

Categorical variables were reported as numbers and percentages and were compared using the Chi-square test. Continuous variables were reported as mean and standard deviation (SD) and were compared using independent sample *t*-test. Statistical analyses were performed using SPSS v24.0 and P values < 0.05 were considered significant.

RESULTS

From the UMMC muscle biopsy databank, 338 patients were diagnosed to have inflammatory myopathy. ENMC subtype classification were as follows: 138 (40.8%) dermatomyositis (DM)

(of which 63 (42.7%) were juvenile DM and 75 (57.2%) adult DM); 80 (23.7%) IMNM; 37 (10.9%) polymyositis; 33 (9.8%) overlap myositis (including six with anti-synthetase syndrome) and 19 (5.6%) inclusion body myositis. 32 (9.5%) remained classified as nonspecific myositis.

From 2012 to 2016, there were 35 IMNM patients in whom serological analyses for anti-SRP and anti-HMGCR autoantibody were done. Twenty six (74.3%) were women with mean age of 37.1 ± 17.0 years (range 8-76 years) (Table 1). Sixteen (45.7%) were positive for anti-SRP, 7 (20.0%) were positive for anti-HMGCR antibodies and 10 (28.6%) were negative for both, while two further patients were positive for both antibodies (dual positivity, 5.7%). IMNM was found in all main ethnic groups in Malaysia and included Malays, 15 (42.9%); Chinese, 15 (42.9%); Indians, 2 (5.7%) and other ethnicities, 3 (8.6%).

Clinical features

The majority of patients (23, 65.7%) presented subacutely. At presentation, all (100%) had proximal muscle weakness while 7 (20%) also had distal muscle weakness. Muscle weakness was severe (MRC ≤ 3) in 22 (62.9%) patients. The lower limbs were more affected than the upper limbs. Most had symmetrical weakness but 2 (5.7%) patients showed asymmetrical involvement. Muscle wasting was noted in 12 (34.3%) patients and 13 (37.1%) patients reported myalgia. Neck flexor weakness was found in 17 (48.6%) patients and dysphagia in 11 (31.4%). Only seven (20%) patients had a history of prior statin use, simvastatin in 6 and atorvastatin in one. Respiratory involvement was found in 4 (11.4%) patients. Two required invasive ventilation, one patient who had presented acutely with severe generalised muscle weakness while the other had chronic severe progressive weakness. In another patient who was anti-SRP antibody positive, HRCT of the chest showed interstitial lung disease (ILD) while another had exertional dyspnoea but was not investigated further. None of the patients in our cohort had cardiac involvement.

Extramuscular manifestations were reported in nine (25.7%) patients and included seven (20%) with cutaneous involvement, one with arthritis and one with both rash and arthralgia. Skin manifestations included one each with discoid lupus and morphea of the right upper limb, and three with photosensitive rash of the face and limbs and 2 with non-specific maculopapular rash. Of these, 4 were anti-HMGCR positive, 2 anti-SRP positive and one, seronegative. An associated connective tissue disease (CTD) was diagnosed in 4 (11.4%) cases (3 anti-SRP positive and one anti-HMGCR positive), one each with systemic lupus erythematosus (SLE), limited scleroderma, rheumatoid arthritis and Sjögren syndrome. No patient had associated malignancy.

Laboratory results

Electromyography was performed in 29 patients and in 28 (96.6%), there were features consistent with an active myopathic process. At its peak, the mean serum CK was 15,632 ± 27,728 U/L (range 150-150000 U/L). Only two (5.7%) patients had a peak CK less than 1,000 U/L. CRP was raised in 6 (35.3%) of 17 patients and ANA was positive in 9 (25.7%) of 20 patients tested. Other myositis antibodies were positive in 19 (54.3%) and included anti-Ro52, 11 (31.4%); anti-Ku, 4 (11.4%); anti-PM/Scl-75 and PM/Scl-100, 3 (8.6%) and anti-PL7 and anti-synthetase (PL7 and PL12) antibodies, 4 (11.4%).

MRI muscle was carried out in only 5 patients. Hyperintensity on STIR sequences was found in 3 (2 seronegative and one anti HMGCR positive) while muscle atrophy was seen in 2 (one each seronegative and anti-HMGCR positive).

In all subjects muscle histopathology showed necrotic muscle fibers with varying degrees of reactive mononuclear cell infiltration (Figures 1 and 2). Three (8.6%) showed moderate degree of inflammation (Figure 1D). MHC-1 staining was positive in 20 (83.3%) of 24 biopsies. This was widespread in 13/20 (65%) and focal and patchy in 7/20 (35%), (Figures 1C and 2B). Membrane attack complex (MAC) immunostaining was not done.

Treatment and outcome

Immunosuppressive therapy was not standardized but depended on the individual physician. Of the 31 patients in whom information was available, 3 did not receive immunosuppressive therapy; 2 had associated severe sepsis at presentation and died while another defaulted follow-up. In the remaining 28 patients, the median interval between onset of weakness and initiation of therapy was 4.5 months (range 1-42 months). All patients (100%) were treated with oral corticosteroids (prednisolone), 23 (82.1%) in combination with at least another immunosuppressive agent. These include methotrexate, azathioprine, mycophenolate mofetil, rituximab, intravenous immunoglobulin, cyclophosphamide and cyclosporine (Table 1).

Table 1: Demographics, clinical features, laboratory data and treatment outcomes of Malaysian immune-mediated necrotizing myopathy (IMNM) patients

Findings, N (%)	**Total (N = 35)**
Age at onset (years)	37.1 ± 17.0 (Range 8-76 years)
Gender	
Female	26 (74.3%)
Male	9 (25.7%)
Ethnicity	
Malay	15 (42.9%)
Chinese	15 (42.9%)
Indian	2 (5.7%)
Others	3 (8.6%)
IMNM specific antibody	
Anti-SRP positive	16 (45.7%)
Anti-HMGCR positive	7 (20%)
Anti-SRP + anti-HMGCR positive	2 (5.7%)
Both negative	10 (28.6%)
Statin exposure	7 (20%)
Subacute onset (≤ 6 months)	23 (65.7%)
Muscle weakness	
Severe (MRC ≤ 3)	22 (62.9%)
Proximal weakness	35 (100%)
Distal weakness	7 (20%)
Pattern of weakness	
LE > UE	24 (68.6%)
UE > LE	1 (2.9%)
UE = LE	10 (28.6%)
Asymmetry	2 (5.7%)
Muscle wasting	12 (34.3%)
Myalgia	13 (37.1%)
Neck weakness	17 (48.6%)
Dysphagia	11 (31.4%)
Extra-skeletal muscle involvement	
Cardiac involvement	0 (0%)
Respiratory involvement	4 (11.4%)
Skin involvement	7 (20%)
Arthralgia	2 (5.7%)
Associated disorders	
Connective tissue disease	4 (11.4%)
Malignancy	0 (0%)
Laboratory investigations	
Myopathic EMG	28/29 (96.6%)

CK (U/L)	15632 ± 27728 (Range 150-150000)
Association with other MAA/MSA	19 (54.3%)
Raised CRP (≥ 1 mg/dL)	6/17 (35.3%)
Positive ANA (≥ 1:160)	9/20 (25.7%)
MHC Class 1 positive on muscle biopsy	20/24 (83.3%)
Treatment (n=28)	
Prednisolone	28 (100%)
Azathioprine	8 (28.6%)
Methotrexate	19 (67.9%)
Mycophenolate mofetil	3 (10.7%)
IVIG	3 (10.7%)
Rituximab	4 (14.3%)
Cyclosporine	1 (3.6%)
Cyclophosphamide	1 (3.6%)
≥ 2 Immunosuppressive medications	23/28 (82.1%)
Neurological outcome (n = 28)	
mRS 0-1	14 (50%)
mRS 2	6 (21.4%)
mRS 3-5	6 (21.4%)
mRS 6 (Dead)	2 (7.1%)

ANA, antinuclear antibody; CK, creatine kinase; CRP, C-reactive protein; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IMNM, immune-mediated necrotizing myopathy; LE, lower extremities; UE, upper extremities; MHC, major histocompatibility complex; mRS, modified Rankin scale; MAA, myositis associated antibody; MSA, myositis specific antibody; SRP, signal recognition particle

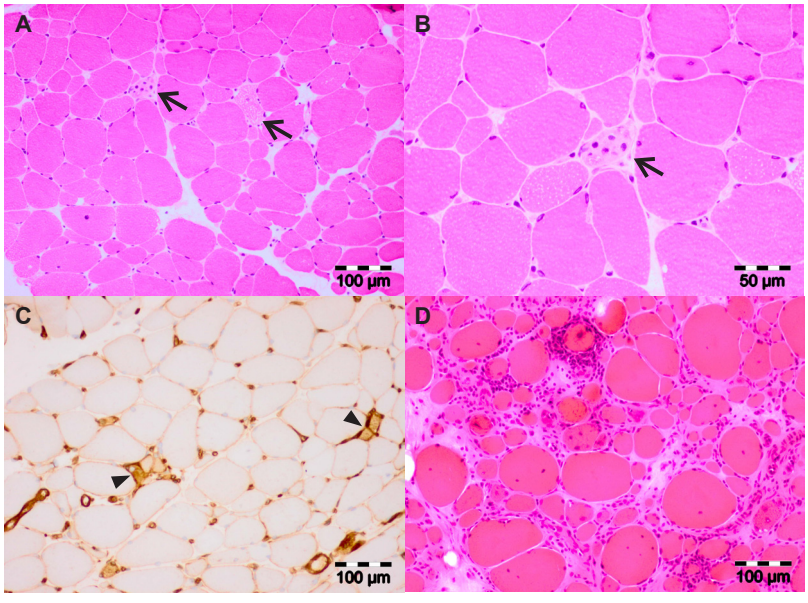

Figure 1. (A & B) H&E staining reveals a typical morphology (arrows) of anti-SRP myopathy. (C) MHC-I positive fibers (arrow heads). (D) Morphology of A13/010 where marked variation in muscle fiber size, necrosis, degeneration and moderate inflammation are noted. Original magnification: x 10 objective (A, C & D); x 20 objective (B)

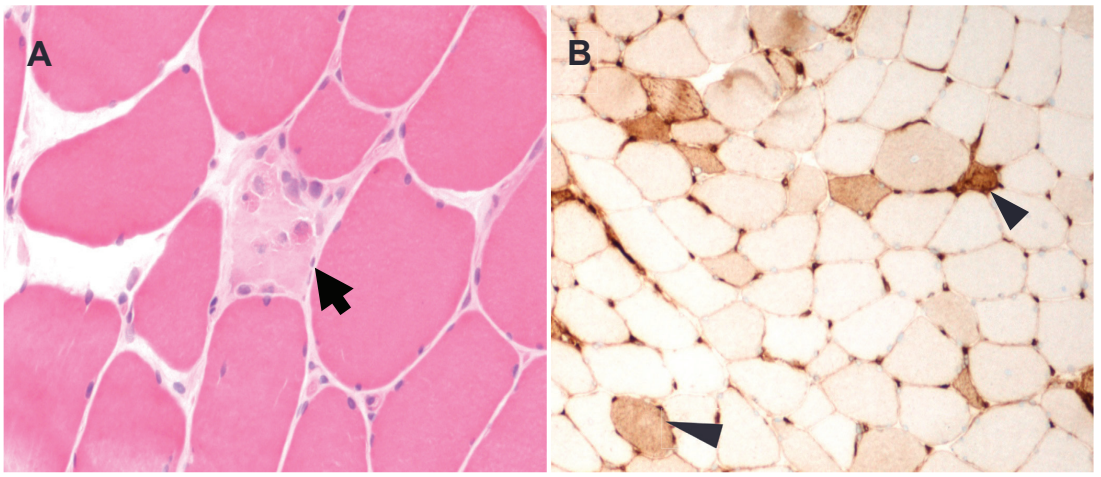

Figure 2. (A) H&E staining showing muscle fiber undergoing necrosis (arrow) in a patient with anti-HMGCR myopathy seen in our series. (B) Degenerating/necrotic fibers stained positive by the major histocompatibility complex (MHC) class-1 (arrows). Original magnification: x 20 objective (A) and x 10 objective (B)

Outcome data were available in 28 patients. Based on the mRS, 14 (50%) patients had marked improvement or had returned to baseline (mRS = 0 or 1), 6 (21.4%) had partial improvement with mild deficit (mRS = 2), and 6 (21.4%) had moderate to severe deficit (mRS = 3-5). Two (7.1%) died from sepsis which was thought to be related to the underlying severe disease.

Comparison between IMNM antibody subtypes

A comparison was made between patients with positive anti-SRP, positive anti-HMGCR and those who were seronegative. Patients who were positive for two antibodies were excluded from comparison analysis. There were no significant differences in terms of gender, ethnicity, age and statin use. Prior statin use was seen in only one (14.3%) anti-HMGCR positive case (Table 2). There were also no differences in terms of disease presentation, severity and pattern of muscle weakness between the groups and neurological outcome. However, muscle wasting was noted significantly more often in the anti-SRP positive group compared to other subtypes (P=0.012) while anti-HMGCR positive patients had more cutaneous involvement (P=0.032). More anti-SRP positive patients had other (non-IMNM specific) myositis antibodies (P=0.007), including the 3 anti-SRP patients with associated CTD. Of the 2 patients with dual antibody positivity; one had mild weakness with good outcome while the other had severe weakness, respiratory failure and subsequently died.

DISCUSSION

In a cohort of Malaysian inflammatory myopathy patients, IMNM was the second most common subtype (after DM) and made up 23.7% of cases. In a series of 35 cases, anti-SRP and anti-HMGCR autoantibodies were positive in 45.7% and 20% respectively, while 28.6% seronegative for both. A further two (5.7%) cases were positive for both antibodies. Our IMNM patients had a wide range of age of presentation (mean 37.1 ± 17.0 years) and significant female predominance (74.3%). Most patients presented subacutely (< 6 months), with severe weakness, predominantly proximal and in lower limbs. CK was typically markedly elevated. Neck flexion weakness was noted in almost half of the patients, dysphagia and distal weakness in about a third and a fifth respectively. These findings are consistent with previously reported IMNM case series.[7-11] IMNM was seen in all major ethnic groups that make up the Malaysian population with no ethnic predilection to severe disease unlike some other multi-ethnic cohorts.[14,22]

When comparing between the different IMNM subtypes, we found no differences in terms of demographic and clinical features. Our anti-SRP positive IMNM patients had significantly more muscle wasting and the anti-HMGCR positive group had more skin involvement. Associations with CTD were uncommon (11.4%) but the associated CTDs, viz. SLE, rheumatoid arthritis, scleroderma, Sjögren syndrome, have been previously noted; in a case series anti-SRP negative patients, SLE was thought to be common.[7,11,15] However, our IMNM patients with CTD were all seropositive (3 anti-SRP and one

Table 2: Comparison between anti-SRP positive, anti-HMGCR positive and seronegative patients

Findings, n (%)	Anti-SRP (n=16)	Anti-HMGCR (n=7)	Both negative (n=10)	P value
Age at onset (years)	40.3 ± 15.4	32.6 ± 13.8	33.4 ± 20.1	0.472
Gender				
Female	14 (87.5%)	4 (57.1%)	7 (70%)	0.259
Male	2 (12.5%)	3 (42.9%)	3 (30%)	
Ethnicity				
Malay	8 (50%)	4 (57.1%)	3 (30%)	0.328
Chinese	7 (43.8%)	1 (14.3%)	6 (60%)	
Indian	0 (0%)	2 (28.6%)	0 (0%)	
Others	1 (6.3%)	0 (0%)	1 (10%)	
Statin exposure	3 (18.8%)	1 (14.3%)	2 (20%)	0.953
Subacute onset (≤ 6 months)	10 (62.5%)	5 (71.4%)	5 (50%)	0.298
Severe weakness (MRC ≤3)	10 (62.5%)	5 (71.4%)	5 (50%)	0.319
Muscle wasting	9 (56.3%)	2 (28.6%)	0 (0%)	0.012*
Myalgia	5 (31.3%)	4 (57.1%)	4 (40%)	0.504
Associated CTD	3 (18.8%)	1 (14.3%)	0 (0%)	0.355
Skin involvement	2 (12.5%)	4 (57.1%)	1 (10%)	0.032*
Discoid Lupus	1	0	0	
Morphea	0	1	0	
Facial photosensitive rash	1	1	1	
Limb photosensitive rash	0	1	0	
Non-specific rash	0	1	0	
Serum CK (U/L)	6708 ± 4848	22145 ± 24053	28500 ± 45462	0.138
Associated MAA/MSA	13 (81.2%)	1 (14.3%)	4 (40%)	0.007*
MHC Class 1 positivity	5/8 (62.5%)	5/5 (100%)	9/10 (90%)	0.158
Poor outcome (mRS ≥ 3)	5/15 (33.3%)	2/5 (40%)	0/4 (0%)	0.358

NB. Two cases with dual antibody positivity were excluded from analyses.
* Statistically significant
CK, creatine kinase; CTD, connective tissue disease; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; MHC, major histocompatibility complex; MAA, myositis associated antibody; MSA, myositis specific antibody; mRS, modified Rankin Scale; SRP, signal recognition particle

anti-HMGCR positive); in contrast to a recent study which reported CTD and extramuscular involvement to be more common in seronegative cases.[16] A higher frequency of associated rheumatic disease with anti-SRP positive group was also noted in a previous series.[11] In addition, more of our anti-SRP group were positive for other myositis antibodies and could suggest an increased tendency to autoimmunity in this group.

Seronegative or anti-HMGCR positive IMNM patients were reported to have higher risk for cancer but none of our IMNM patients were found to have any associated malignancy.[17] Cardiac involvement has been noted in anti-SRP positive group.[3] However, again this was not seen in our cohort and was also rare in a larger Japanese series, suggesting that may be less common among Asian IMNM patients.[3,7,11] However, we could not completely exclude the possibility of cardiac abnormalities in our patients as we did not routinely carry out cardiac investigations e.g. echocardiography for all our patients. Similarly, respiratory involvement was also uncommon in our patients. Respiratory involvement was

reported in four (11.4%) of our patients; 2 of which were due to severe disease and respiratory muscle weakness. ILD was confirmed in one anti-SRP positive case by HRCT. ILD changes are considered to be mild, mainly in the anti-SRP positive group and possibly thought to be related to respiratory muscle weakness.[2,3,11] Overall, the justifications for routine cardiac and respiratory screening in our cohort is unclear but as consequences of involvement, especially cardiac, may be severe, it may be prudent to routinely check for symptoms and to have a lower threshold for tests.

Statin use has been associated with an increased risk of developing anti-HMGCR necrotizing myopathy.[7, 9,18] However, only one anti-HMGCR patient in our cohort had prior statin exposure and there was no significant difference between IMNM subtypes with regards to prior use of statins. Statin-naïve anti-HMGCR patients may be not uncommon and could be seen more often in amongst Asian cohorts.[19-21]

Generally, IMNM is regarded as poorly responsive to conventional immunotherapy.[3,7,11,22] The majority of our patients (82.1%) required combination of at least two immunosuppressive drugs including corticosteroids. However, neurological outcome data showed 50% of our patients improved and had minimal or no disability (mRS 0-1); while almost a third of our patients had significant disability (mRS ≥ 3) and two died. This is similar with other cohorts in which there was significant proportion of patients with persistent disability despite aggressive immunotherapy.[11,14,22] Poor prognostic factors that have been reported include anti-SRP positivity and in this group, younger age group and ethnicity in certain populations (viz. African Americans and Aboriginals and Torres Islanders). The degree of complement activation on muscle histopathology has also been reported as a marker for severe disease.[14,22]

In the current study, there were 2 patients who were positive for anti-SRP and anti-HMGCR antibodies. While there have been a few cases of dual positivity reported previously, its significance and explanation is unknown.[7,11] However, as anti-SRP antibodies were tested using RNA immunoprecipitation, which is believed to be a more reliable method than ELISA, we could not exclude the possibility of anti-HMGCR antibody false positivity in these two patients.

The main limitation of this study is its relatively small sample size coming from a single centre. However, it provides a description of IMNM in a multi-ethnic Asian population which is generally consistent with the findings of IMNM from other populations. Other limitations include the incomplete outcome data, as a number of the patients were referred to us for confirmation of diagnosis but subsequently treated and/or lost to follow-up from their respective primary hospitals. Another limitation was the unavailability of MAC immunohistochemistry.

In conclusion, in a cohort of Malaysian inflammatory myopathy patients, IMNM was the second most common subtype after DM. Of the different IMNM subgroups, anti-SRP positive IMNM was the commonest followed by seronegative and anti-HMGCR positive groups respectively. Anti-SRP positive group had greater muscle wasting, suggesting more severe disease. Cardiac involvement was not found and respiratory involvement was rare and mild. On the other hand, statin use was uncommon in our anti-HMGCR group. The majority required an additional immunosuppressant to corticosteroids and about a third of IMNM patients had a poorer outcome with persistent disability.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Allenbach Y, Benveniste O. Acquired necrotizing myopathies. *Curr Opin Neurol* 2013; 26: 554-60.
2. Day J, Limaye V. Immune-mediated necrotising myopathy: A critical review of current concepts *Semin Arthritis Rheumat* 2019; 49: 420-9.
3. Allenbach Y, Mammen AL, Benveniste O, *et al*. 224th ENMC international workshop: clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. *Neuromuscul Disord* 2018; 28: 87-99.
4. Tanboon J, Nishino I. Classification of idiopathic inflammatory myopathies: pathology perspectives. *Curr Opin Neurol* 2019, 32: 704-14.
5. Stenzel W, Goebel H-H, Aronica E. Review: immune-mediated necrotizing myopathies – a heterogenous group diseases with specific myopathological features: immune mediated necrotizing myopathies. *Neuropathol Appl Neurobiol* 2012; 38: 632-46.
6. Anquetil C, Boyer O, Wesner N, Benveniste O, Allenbach Y. Myositis-specific autoantibodies: a cornerstone in immune-mediated necrotizing myopathy. *Autoimmun Rev* 2019; 18(3): 223-30.
7. Kassardjian CD, Lennon VA, Alfugham NB, Mahler M, Milone M. Clinical features and treatment outcomes of necrotizing autoimmune myopathy. *JAMA Neurol* 2015; 72(9): 996-1003.

8. Suzuki S, Hayashi YK, Kuwana M, *et al*. Myopathy associated with antibodies to signal recognition particle: disease progression and neurological outcome. *Arch Neurol* 2012; 69: 728-32.
9. Ramanathan S, Langguh D, Hardy TA, *et al*. Clinical course and treatment of anti-HMGCR antibody-associated necrotizing autoimmune myopathy. Neurol Neuroimmunol Neuroinflamm 2015; 2(3): e96
10. 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.
11. Watanabe Y, Uruha A, Suzuki S, *et al*. Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. *J Neurol Neurosurg Psychiatry* 2016; 87: 1038-44.
12. Hoogendijk JE, Amato AA, Lecky BR, *et al*. 119th ENMC international workshop: Trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10–12 October 2003, Naarden, The Netherlands. *Neuromuscul Disorders* 2004;14:337-45.
13. Rose MR. 188th ENMC International Workshop: inclusion body myositis, 2 – 4 December 2011, Naarden, The Netherlands. *Neuromuscul Disord* 2013; 23: 1044-55.
14. Day J, Otto S, Cash K, Limaye V. Clinical and histological features of immune-mediated necrotising myopathy: A multi-centre South Australian cohort study. *Neuromuscul Disorders* 2020; 186-99.
15. Ellis E, Ann Tan J, Lester S, et al. Necrotizing myopathy: clinicoserologic associations. *Muscle Nerve* 2012; 45: 189-94.
16. Lim J, Rietveld A, De Bleecker JL, et al. Seronegative patients form a distinctive subgroup of immune-mediated necrotizing myopathy. *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e513.
17. Allenbach Y, Keraen J, Bouvier A-M, *et al*. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. *Brain* 2016; 139; 2131-35.
18. Mammen AL, Chung T, Christopher-Stine L, *et al*. Antoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. *Arthritis Rheum* 2011; 63: 713-21.
19. Allenbach Y, Drouot L, Rigolet A, *et al*. French Myositis Network. Anti-HMGCR autoantibodies in European patients with autoimmune necrotizing myopathies: inconstant exposure to statin. *Medicine* (Baltimore) 2014; 93: 150-7.
20. Ge Y, Lu X, Peng Q, Shu X, Wang G. Clinical characteristics of anti-3-hydroxy-3-methylglutaryl coenzyme A reductase antibodies in Chinese patients with idiopathic inflammatory myopathies. *PLOS One* 2015; 2015; 10(10): e0141616.
21. Jiao Y, Cai S, Lin J, *et al*. Statin-naïve anti-HMGCR antibody-mediated necrotizing myopathy in China. *J Clin Neurosci* 2018; 57: 13-9.
22. Pinal-Fernandez I,Parks C, Werner J, *et al*. Longitudinal course of disease in a large cohort of myositis patients with autoantibodies recognizing the Signal Recognition Particle. *Arthritis Care Res* 2017; 69(2): 263-70.