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Profile of various idiopathic inflammatory myopathies at two university hospitals in Yangon, Myanmar

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Abstract

Objective: to determine the distribution of various idiopathic inflammatory myopathies (IIM) and their profile at the largest university hospitals in Yangon, Myanmar. *Method:* It was a hospital based prospective study recruiting IIM patients admitted to Neurology and Rheumatology ward over a 1.5 year period from September 2017 to February 2019. *Results:* Among total 51 IIM patients recruited, 62.7% presented to Neurology ward and 37.3% to Rheumatology ward. Overlap myositis (OM) was the commonest (43%), followed by immune-mediated necrotizing myopathy (IMNM) 27%, dermatomyositis (DM) 24%, polymyositis (PM) 6%. Among OM, anti-synthetase syndrome (ASS) was 23%, and among IMNM, anti-SRP positive was 79%. IMNM and PM patients presented more to neurologists while OM/ASS and DM more to rheumatologists; 82% were females (F:M= 4.6:1). Mean age of onset of myositis was 40.2 ± 17.8 years, and duration of symptoms before presentation was 10-3,600 days (shortest in anti-SRP and longest in anti-HMGCR myopathy). Myositis antibodies were positive in 67%. CK range was 40-25,690 U/l, highest in IMNM and lowest in DM. Associated connective tissue diseases among OM in order of descending frequency were 47% systemic lupus erythematosus, 24% Sjogren syndrome, 41% scleroderma and 12% rheumatoid arthritis. Associated cancer identified were one lung cancer in DM, one breast cancer in OM, one buccal cancer in IMNM cases.

Conclusions: With recent availability of myositis antibody panel and MHC staining in Myanmar, we have applied current updated classification to describe the first Myanmar data on IIM cases.

Keywords: Idiopathic inflammatory myopathies, antibodies, muscle biopsy

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) consist of a heterogeneous group of chronic systemic autoimmune diseases mainly presenting with inflammation of skeletal muscles and has high morbidity and disability. In 20th century, classification had been very simple: myositis with typical cutaneous changes as dermatomyositis and without cutaneous changes as polymyositis[1], with additional category of inclusion body myositis (IBM) since 1995. In 21st century, with newly identified IIM subtypes such as immune-mediated necrotizing myopathy (IMNM) and anti-synthetase syndrome (ASS), IIM has been recently classified as polymyositis (PM), dermatomyositis (DM), IBM, IMNM and overlap myositis (OM) including ASS.[2,3] As a disease of autoimmunity, these are found to be associated with a variety of myositis antibodies, the number of which are also of expanding list and newer clinical and pathological associations have been discovering with time.

In Myanmar, because of limited facilities in the past and the cost, the spectrum of various IIM has not been studied yet. Recently, myositis autoantibodies panel can be tested locally and muscle biopsy services with specimen preparation and staining have been improved. Hence, this study has been aimed to find out the profile of various IIM patients at the largest tertiary University hospitals in Myanmar (Neurology department, Yangon General Hospital (YGH), and Rheumatology department, Yangon Specialty Hospital (YSH)).

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METHODS

This was the collaborative cross sectional descriptive study among Departments of Neurology and Pathology of YGH and Department of Rheumatology of YSH, which are both departments under the University of Medicine 1. Consecutive myositis patients who gave informed consent and who fulfilled the inclusion criteria of IIM (acute or subacute onset proximal myopathy, normal or high creatinine kinase (CK), myopathic units in electromyogram (EMG) and/or muscle biopsy consistent with inflammatory myositis after elimination of other causes of myopathy such as metabolic and infections) were recruited prospectively over a period of one and a half year period from September 2017 to February 2019. Their clinical presentations and severity were recorded, and serum was tested for myositis autoantibodies panel (by Euroline myositis profile 3 (IgG) test kit). Muscle biopsy was performed, prepared with paraffin and frozen sections, stained with hematoxylin and eosin, modified Gomori Trichrome (mGT) and MHC immunochemical staining. Variable combinations of clinical, serological, and pathological information were used to subclassify; DM: presence of skin lesions including heliotrope rash, periorbital edema, Gottron papules, Gottron sign, V-sign, shawl sign and/or serological evidence of anti-Mi-2 and/or pathological findings of perifascicular necrosis, perimysial connective tissue fragmentation, perifascicular atrophy (PFA), IMNM: pathological findings of necrotic and regenerating fibers without or sparse inflammation and/or serological evidence of anti-SRP or anti-HMGCR antibody, OM: overlap with other connective tissue disorders (CTD) including ASS, ASS: one of the tested antisynthetase antibodies such as anti-Jo-1, PL-7, PL-12, EJ, OJ with variable combined clinical features of interstitial lung disease (ILD), mechanic hands, arthritis, Raynaud phenomenon, fever, and/or pathologically perifascicular necrosis, perimysial connective tissue fragmentation and/or PFA, IBM: clinical pattern of asymmetrical weakness mainly affecting knee extensors and finger flexors and pathology showing endomysial lymphocytic invasion surrounding or invading in non-necrotic fibers and rimmed vacuoles on mGT stain, pure PM: primary endomysial inflammation after excluding DM, IMNM and OM/ASS.[2,3]

Statistical analysis

Data entry and analyses were done by Microsoft excel 2010. Categorical variables were summarized in proportions, and numerical variables were described in means (SD).

Ethical Considerations

This study was submitted and approved by the Research and Ethics Committee of the University of Medicine (1), Yangon (089/UM, REC.2018).

RESULTS

Mean age of IIM patients was 44.6 ± 14.5 years and 82% were females. Mean age of onset of myositis was 40.2 ± 17.8 years. Duration of symptoms before presentation ranged from 10-3,600 days (shortest in anti-SRP associated IMNM and longest in anti-HMGCR associated IMNM). Serum CK range was 40-25,690 U/L (lowest in OM and highest in anti-SRP associated IMNM). Regarding muscle weakness, mean MRC sum score was 44 ± 8. Table 1 shows the distribution of IIM types. Among OM, one-fourth was ASS, and among IMNM, nearly 80% were anti-SRP antibody positive. Clinico-pathological presentations of different IIM types are shown in Table 2. Among four main types of IIM collected

Table 1: Distribution of IIM subtypes among study population

	Neurology ward	Rheumatology ward	Total
IMNM	13 (41%)	1 (5%)	14 (27%)
OM	12 (38%)	10 (53%)	22 (43%)
DM	4 (13%)	8 (42%)	12 (24%)
PM	3 (9%)	0 (0%)	3 (6%)
Total	32 (62.7%)	19 (37.3%)	51 (100%)

IIM Idiopathic inflammatory myopathies
IMNM Immune-mediated necrotizing myopathy
OM Overlap myositis
DM Dermatomyositis
PM Polymyositis

Table 2: Clinico-pathological presentations of different IIM subtypes

Types of IIM	IMNM	OM/ASS	Pure DM	Pure PM
No (%)	14	22	12	3
Mean age (years)	39 ± 14	45 ± 12	46 ± 20	55 ± 8
Gender (F:M)	3.7:1	11:1	11:1	2:1
Mean age of onset (years)	37 ± 17	45 ± 12	46 ± 20	50 ± 16
Mean duration of symptoms at home before admission (days)	351 (71 in SRP and 3600 in HMGCR)	138	99	205
MRC sumscore (severity of muscle weakness)	43 ± 7	43 ± 9	48 ± 6	43 ± 8
Systemic features				
Fever	14%	100%	25%	0
Weight loss	43%	50%	42%	0
Bulbar	29%	14%	33%	33%
Neck weakness	43%	5%	8%	67%
Arthralgia	7%	64%	42%	0
Arthritis	0	27%	25%	0
Skin rash	0	27%	92%	0
Raynaud Mechanic	0	18%	17%	0
hands	0	5%	8%	0
ILD	0	14%	8%	0
Myocarditis	0	23%	0	0
Co-morbidities	1 HBV	1 AIHA, 1 AIH, 2 hypothyroidism, 1 MG, 1 HBV, 1 HCV		1 MG, 1 ASD
Associated connective tissue diseases		2 RA, 8 SLE, 7 Scleroderma, 4 Sjogren		
Associated cancer	1 Buccal cancer	1 Breast cancer	1 lung cancer	
Mean serum CK level (U/L)	9358	4497	2293	4189
Myositis antibody	SRP, HMGCR	Ro-52,Ku, PM-Scl /PL-7, Jo-1	Mi-2	Ku, PM-Scl75
Muscle biopsy findings	93% IMNM 7% normal	82% PM, 9% DM, 9% IMNM	100% DM	100% PM

ASS Anti-synthetase syndrome
F Female
M Male
SRP signal recognition particle
HMGCR 3-hydroxy-3-methylglutaryl-CoA reductase
MRC (Medical Research Council) sumscore for muscle weakness (0 total paralysis, 60 normal)
ILD Interstitial lung disease
HBV Hepatitis B virus infection
AIHA Autoimmune hemolytic anaemia
AIH Autoimmune hepatitis
MG Myasthenia Gravis
HCV Hepatitis C virus infection
ASD Atrial septal defect
RA Rheumatoid arthritis
SLE Systemic lupus erythematosus

in this study, PM cases were relatively older whereas IMNM cases were younger. Severity of limb weakness by MRC sumscore was comparable between all types. Systemic manifestations such as fever, arthralgia, ILD and carditis were more common in OM/ASS subtype whereas IMNM subtype has less extramuscular involvement apart from constitutional symptoms. Dermatological manifestations were more common in DM. Neck weakness was noted more in IMNM and PM, which may indicate severity. Undoubtedly, OM associated more with other systemic autoimmune diseases and connective tissue diseases.

Table 3 describes their clinico-pathological profile of tested myositis antibodies. Myositis antibodies were positive in 67% of IIM cases, which, in order of descending frequency, were anti-SRP (21%), anti-Ro-52 (16%), anti-Ku (12%), anti-PL-7 (8%), anti-Jo-1, anti-Mi-2 and anti-PM-Scl75 (4% each), anti-PM-Scl100 and anti-HMGCR (2% each), and anti-PL-12, anti-EJ and anti-OJ (0%). Patients with anti-HMGCR and anti-SRP antibodies presented as IMNM, Anti-Jo1, anti-PL-7 as ASS, anti-Ro-52, anti-Ku and anti-PM-Scl as OM and anti-Mi-2 in DM cases. Age of onset was under 40 years in anti-HMGCR, anti-Mi-2, anti-Ku and anti-Ro-52 associated IIM, and over 40 years in anti-PM-Scl, anti-SRP, anti-Jo-1 and anti-PL-7. Females were affected more regardless of antibody types. Shortest mean duration of symptoms before presentation, more neck weakness with higher serum CK level in anti-SRP myositis might depict its more acute nature of onset and severity. Duration was longest in anti-HMGCR myositis and it can mimic inherited muscular dystrophy. Mean duration before presentation was mostly subacute under 6 months except one PM-Scl100 case who presented after 8 months and one anti-HMGCR case presented with 10 years duration. Anti-Ku myositis had lowest MRC sumscore (38) whereas highest score in anti-Jo-1 myositis. Regarding systemic manifestations, fever was seen in at least half of anti-Mi-2, anti-Jo-1 and anti-Ro-52 cases, weight loss was commonly seen in anti-HMGCR, anti-Ro-52 and anti-PL-7. Neck weakness was seen mainly in anti-SRP and anti-HMGCR myopathies, which might indicate their severity and possibility of later respiratory muscle involvement. Arthralgia was noted in more than half of anti-Jo-1, anti-PL-7 and anti-Ku. As for dermatological manifestations, skin rash was seen in at least 50% of anti-PM-Scl100, anti-Jo-1 and anti-Mi-2, less (13-25%) in anti-PL-7, anti-Ku and anti-Ro-52, Raynaud phenomenon in 50% of anti-Jo-1 and anti-PL-7 and mechanic hands in 50% of anti-Jo-1. ILD was identified in 50% of anti-Jo-1 and anti-PM-Scl75, 13-25% of anti-Ro-52 and anti-PL-7, and carditis in 50% of anti-Jo-1 and 13-25% of anti-PL-7, anti-Ku, anti-Ro-52 cases. Antibodies associated with other systemic autoimmune diseases and CTD were anti-Ku, anti-PM-Scl75, anti-PM-Scl100 and anti-Ro-52. CK level was highest in anti-SRP and lowest in anti-Jo1. Concerning muscle biopsy findings, all anti-Mi-2 cases had DM histological features, anti-PM-Scl75 and anti-PM-Scl100 cases had PM histological features, all anti-SRP and anti-HMGCR biopsies had IMNM histological features, while anti-Ro-52 and Ku had more PM, anti-PL-7 had more DM, and anti-Jo-1 had half DM and half PM histological features. Among 17 vitamin D tested cases, 82% were found to be deficient, which reminded us the need to screen for Vitamin D deficiency in IIM and manage accordingly.

DISCUSSION

Since myositis patients could present to both neurologists and rheumatologists, this study was done at both Neurology and Rheumatology ward. Among total 51 IIM patients recruited, 62.7% were from Neurology ward and 37.3% from Rheumatology ward. IIM cases presented to neurologists were more of IMNM and PM while those presented to rheumatologists were more of OM and DM. Mean age at examination was 44.6 + 14.5 years. Mean age was 30.4 years in an India study[4], 55.2 years in a Japan study[5], and 49.37 and 44.53 years in IIM with myositis specific antibodies (MSAs) and without MSAs respectively in a China study.[6] However, this is difficult to compare because our study was done only in adult hospital with patients over 12 years of age, whereas above three other studies recruited all ages including children. But our patients still had lower mean age than Japan and China even without juvenile, which could be explained by the fact that life expectancy in Myanmar is far lower than Japan and China. Female to male ratio was 4.6:1 in current study but it was 1.3:1 in Japan study[7] and 1.4-2.2:1 in China study.[6] Although all agree that IIM affects females more, the ratio variation may be accounted for by geographical variation and ethnicity. OM/ASS was the commonest (43%), followed by IMNM (27%), DM (24%) and PM (6%). It agrees with the current belief that OM, DM, and IMNM accounted for 90% of IIM with commonest OM

Table 3: Myositis antibody profile and their clinico-pathological presentations

Myositis antibodies	**Mi-2**	**Ku**	**PM-Scl100**	**PM-Scl75**	**Jo-1**	**SRP**	**Pl-7**	**Ro-52**	**HMGCR**
No (%)	2 (4)	6 (12)	1 (2)	2 (4)	2 (4)	11 (21)	4 (8)	8 (16)	1 (2)
Type of IIM	DM (100%)	OM(67%) PM(17%) IMNM (17%)	OM (100%)	OM(50%) PM(50%)	ASS (100%)	IMNM (100%)	ASS (100%)	OM/ASS (100%)	IMNM (100%)
Mean age (years)	28	34	56	58	45	41	52	37	16
Gender (F:M)	All F	5:1	All F	All F	All F	4.5:1	All F	3:1	All F
Mean age of onset (years)	28	33	36	58	44	42	52	38	6
Mean duration before admission (days)	135	115	240	128	57	71	237	128	3600
MRC sumscore	50	38	48	49	54	46	42	40	44
Systemic features									
Fever	100%	40%	0	0	50%	18%	0	50%	0
Weight loss	50%	40%	0	0	50%	45%	75%	88%	100%
Bulbar	0	40%	0	0	100%	36%	25%	0	0
Neck weakness	0	0	0	0	0	45%	0	38%	100%
Arthralgia	50%	60%	0	0	100%	9%	75%	38%	0
Arthritis	0	20%	0	0	0	0	25%	13%	0
Skin rash	50%	20%	100%	0	50%	0	25%	13%	0
Raynaud Mechanic	0	20%	0	0	50%	0	50%	0	0
hands	0	0	0	0	50%	0	25%	0	0
ILD	0	0	0	50%	50%	9%	25%	13%	0
Myocarditis	0	20%	0	0	50%	0	25%	13%	0
Co-morbidities		AIHA, AIH, Hypo-thyroid	Lichen Amyloid of skin	MG, ASD		HBV	HCV	Hyp-othyroid, AIHA, AIH	
Connective tissue diseases									
Sjogren's syndrome	0	0	0	0	0	18%	0	63%	0
Scleroderma	0	60%	100%	50%	0	0	0	13%	0
SLE	0	40%	0	0	0	0	0	38%	0
Mean serum CK level (U/L)	2643	3568	3650	1649	1028	8968	1980	4960	4506
Pathological diagnosis									
DM**	100%	0	0	0	50%	0	80%	0	0
PM*	0	67%	100%	100%	50%	0	20%	71%	0
IMNM***	0	33%	0	0	0	100%	0	29%	100%

CK Creatinine kinase

* Primary endomysial inflammation (endomysial lymphocyte infiltration surrounding non-necrotic muscle fibers, MHC-1 expression

** PFA, Perifascicular structural abnormalities, MHC-1 expression

***Muscle fiber necrosis and regeneration without primary endomysial inflammation, MHC-1 expression

followed by IMNM and DM[2].However, in Japan study by Watanabe et al, the order was IMNM (39%), IBM (16%), DM 12%, ASS (11%), non-specific myositis (18%), PM (4%).[5] China study, although published in 2019, used the older classification and concluded DM 75.4% and PM 24.5% out of 497 IIM patients, and IMNM and OM/ASS subtypes were not included in their classification.[6] Actually, there are few studies to compare the distribution of various IIM subtypes because most of the earlier studies including above China study based on older classification. In contrast to these studies, we did not identify IBM in our cohort, which supports our traditional belief of lower IBM prevalence in Asians than Westerns, and absent IBM in our study might be due to smaller sample size.

Myositis antibody positivity rate in the current study was 67%, which agrees with 65.4% antibody positivity of China study[6], but it is difficult to compare because they use different antigen subsets. India study by Srivastava *et al*. used the same test kit with same subsets of antigens as our study and found 73.4 % positive, which is higher than our study.[4] India study's distribution was 20.9 %, 23.4 %, 4.8 %, 50.8% for anti-Mi2, anti-synthetase (Jo1, PL7, PL12, EJ, OJ) and anti-SRP, myositis-associated autoantibodies (MAA) (Ro52, Ku, PM-Scl 75, PM-Scl 100) respectively whereas 4%, 12%, 21%, 34% respectively in our study.[4] Regarding the clinical presentations, our findings agree their findings of anti-Mi2's positive association with DM and negative association with ILD, and mechanics' hands being more in patients with anti-synthetase antibodies. In our study, ILD was found in 50% of anti-Jo-1, 50% of anti-PMScl-75, 25% of anti-Pl-7, 13% of anti-Ro-52, and 9% anti-SRP, and 0 in Mi-2, which agree with India study showing ILD significantly more in ASA, not in Mi-2, and China study showing ILD association with anti-Jo-1.[4,6] Anti-SRP IMNM patients in this study are comparable to those in Japan study with clinical characteristics of relatively commoner neck weakness, rarer cardiac and skin involvement, fewer ILD than other IIM types, and rheumatological diseases association of 18% and 12%, mean CK level of 8968 and 6589 U/L respectively.[5] In India study, among 22 patients with CTD myositis, there were 9 patients with scleroderma, 7 with systemic lupus erythematosus (SLE), 4 with mixed CTD (MCTD) and 1 Sjogren's syndrome and 1 undifferentiated CTD (UCTD) [4], whereas in our study, among 21 CTD myositis, 7 were with scleroderma, 8 with SLE, 4 with Sjogren's syndrome and 2 with rheumatoid arthritis (RA). Ungprasert *et al*, on reviewing Asian population studies, found malignancy in 10% of IIM: lung and nasopharyngeal were most common.[8] In our study, malignancy association was 5.9%. Lesser percentage might be explained by cross sectional study design.

In conclusion, with recently available myositis antibody test and MHC-1 immunohistochemical staining in Myanmar, we have applied current updated classification to describe IIM cases in Myanmar. Anti-SRP myositis cases presented as IMNM which were more severe and acute and with less systemic manifestations. All anti-Mi-2 positive cases were DM and found not to be associated with malignancy or ILD. ILD was noted mainly in anti-Jo-1 and anti-PM-Scl75, anti-PL-7 and anti-Ro-52 positive cases. Anti-Ro-52, anti-Ku, anti-PM-Scl, anti-PL-7 and anti-Jo-1 positive cases presented with OM. Our limitations are small sample size limited to adult hospital, limited resources regarding immunology stains and antigen subsets (anti-HMGCR antibody tested only in few suspected cases), and being cross sectional rather than follow up on prognosis. However, we hope this study will be a preliminary step for future study with more antibodies and larger sample size on IIM in Myanmar.

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DISCLOSURE

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