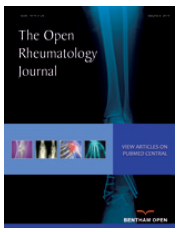

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RESEARCH ARTICLE

Clinical Characteristics of Systemic Sclerosis-associated Myopathy Patients Comparing Different Subgroups of Inflammatory Myopathies

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Abstract:

Background:

Available data regarding clinical characteristics of systemic sclerosis-associated myopathy (SSc-M) patients comparing different subgroups of muscle pathology are limited. We aimed to compare clinical and laboratory findings among different subgroups of Thai patients with SSc-M.

Methods:

From January 2010 to December 2019, 27 patients with suspected SSc-M underwent a muscle biopsy. Twenty-three patients with available frozen muscle biopsy specimens for repeating immunohistochemical stained for reviewing were included. There were three subgroups of pathological findings, including immune-mediated necrotizing myopathy (IMNM), non-specific myopthy (NsM), and polymyositis (PM). No fibrosing myopathy was observed. Baseline clinical data and laboratory findings were compared within those three inflammatory myopathies.

Results:

Of the 23 SSc-M, there were 14 females and 19 DcSSc with a mean age and disease duration of SSc of 53.6±7.7 years and 16.4±23.6 months, respectively. Their mean duration from weakness to muscle biopsy was 3.6±6.0 months. There were 14 (60.9%) patients with IMNM, 6 (26.1%) with NsM, and 3 (13.0%) with PM. At the biopsy date, IMNM had a greater prevalence of severe muscle weakness (42.6% *vs*. 0% *vs*. 0%) and arthritis (87.5% *vs*. 50% *vs*. 0%) than the NsM and PM groups. There was no significant difference among the three inflammatory patterns regarding baseline clinical characteristics, including age, gender, SSc subtype, disease duration, other organ involvements and median values of CK and ESR levels.

Conclusion:

In this study, we found that the pathological findings of Thai SSc-M were IMNM, NsM, and PM. No fibrosing myopathy was observed. SSc with IMNM tended to have more severe baseline muscle weakness and arthritis than the other inflammatory patterns.

Keywords: Immune-mediated necrotizing myopathy, Myositis, Myopathy, Non-specific myopathy, Polymyositis, Systemic sclerosis.

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1. INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease whose etiopathogenesis originates from endothelial injury, autoimmunity, and fibroblast over proliferation, resulting in organ inflammation in an early phase of the disease and then turning to fibro occlusive vasculopathy and organ fibrosis in the late phase of the disease. The hallmark of organ complications of SSc includes skin thickening and visceral organs complications such as gastrointestinal, cardiopulmonary, and muscle involvement, either inflammation or fibrosis, depending on the disease phase [1].

Currently, there has been no consensus classification criteria for systemic sclerosis-associated myopathy (SSc-M). Multiple composite measurements, including proximal muscle weakness, elevated muscle enzyme, myopathic change detected by electromyography, or muscle pathology features, are helpful for diagnosis [2 - 5]. Distinct muscle histological pattern helps distinguish myopathy subtypes [6]. The prevalence of SSc-M varies ranging from 14-79% depending on different criteria of myopathy, different study population, and study design [7].

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SSc-M has a poor long-term outcome, which is associated with cardiopulmonary complications, including interstitial lung disease (ILD), myocardial disease, congestive heart failure (CHF), arrhythmia, and sudden cardiac death [8].

Muscle pathological findings in SSc-M have been reported, including polymyositis (PM), dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), nonspecific myopathy (NsM), fibrosing myopathy (FM), and acute denervation [9]. Two subtypes of histological findings have been described, including (i) fibrosing myopathy (fibrosis pattern) and (ii) inflammatory myopathies (inflammatory pattern), including PM, DM, IMNM or NsM [10]. Although SSc with overlapping myositis is associated with cardiopulmonary complications and lower survival time [11, 12]. Compared with an inflammatory pattern, SSc patients with fibrosing patterns had a higher prevalence of ischemic heart disease, conduction defect or arrhythmias, anti-topoisomerase I antibodies, a greater median ESR and a higher mortality [13].

Published data regarding clinical characteristics and laboratory investigations of systemic sclerosis-associated myopathy (SSc-M) comparing different subgroups of inflammatory patients are still scant in this field. Therefore, we aimed to compare baseline clinical and laboratory findings within different subgroups of Thai patients with SSc-M.

2. METHODS

2.1. Patients

The retrospective study of SSc-M patients seen at the Rheumatology Clinic, Maharaj Nakorn Chiang Mai Hospital, Thailand, between January 2010 and December 2019 was conducted. All adult SSc patients (age ≥ 18 years) fulfilled the 1980 classification criteria of SSc [14] and/or the ACR/EULAR criteria 2013 for the classification of SSc [15]. The diagnosis of SSc-M was defined as the presence of symmetrical proximal muscle weakness, elevated creatine kinase (CK) level without other explainable causes, and muscle biopsy reports compatible with myopathic change either inflammatory or fibrosing pattern. Twenty-seven patients with suspected SSc-M underwent muscle biopsy. Twenty-three of 27 SSc-M with available frozen muscle biopsy specimens for repeating immunohistochemically staining were included. For patients who had multiple muscle biopsies, the first biopsy specimen was used for analysis. Four excluded patients were DcSSc subtype with anti-topoisomerase-I antibody-positive. Clinical and laboratory data at the biopsy date were reviewed. Exclusion criteria were SSc overlapping systemic lupus erythematosus or rheumatoid arthritis or SjÖgren's syndrome or mixed connective tissue disease.

2.2. Methods

The following data were collected from the medical records as described by the physicians as of the date of initial muscle biopsy, including demographic data, disease subtype, modified Rodnan skin score (mRSS); muscle involvement comprised myalgia and muscle strength; other organ involvement was defined as "presence" if we found its recorded data at the biopsy date including hypo-hyperpigmentation, digital ulcer, arthritis, tendon friction rub, dysphagia, gastroesophageal reflux disease (GERD), interstitial lung disease (ILD), suspected pulmonary hypertension (PH), scleroderma renal crisis (SRC) and congestive heart failure (CHF); laboratory testings comprised, creatine kinase (CK), and erythrocyte sedimentation rate (ESR), hemoglobin, and creatinine (Cr).

2.3. Definition of Clinical Features

The SSc subtype was classified as *diffuse cutaneous SSc (DcSSc)* or *limited cutaneous SSc (LcSSc)* according to LeRoy and Medsger's classification criteria [16]. *SSc duration* was defined as the interval from the first non-Raynaud's phenomenon (NRP) contributable to SSc manifestation to undergo muscle biopsy. *Myopathy duration* was defined as the interval from the first muscle weakness to undergoing muscle biopsy. Skin thickening was recorded using a *modified Rodnan skin score (mRSS)* [17]. *Muscle power* was recorded on the 6 grade according to the Medical Research Council scale, which ranges from 0 (muscle weakness with no visible muscle contraction) up to 5 (normal power) [18]. We then divided the muscle power into two subgroups, including (i) severe weakness as proximal muscle power of grade ≤ 2 was classified; and (ii) mild to moderate weakness as muscle power of grade ≥ 3-4. *The digital ulcer* was defined as the presence of active or healed ulceration which is present at the volar aspect of the digital pulp. *Arthritis* was defined as the presence of joint tenderness and swelling examined by attending rheumatologists. Gastrointestinal involvements were defined as the presence of *GERD* or *dysphagia* symptoms. *Interstitial lung disease* (ILD) was determined by chest X-ray or high-resolution computed tomography. *Suspected pulmonary hypertension (PH)* was defined according to the presence of echocardiographic signs suggesting PH according to the 2015 ESC/ERS guideline [19]. *Scleroderma renal crisis* (SRC) was defined as present if the criteria of the International Scleroderma Crisis Study Group were fulfilled [20].

2.4. Muscle Acquisition and Staining Techniques

Frozen muscle biopsy specimens received from 2010 to 2019 were retrieved from a -80 °C tissue bank. Five-micron-thickness cryostat sections were done. Each specimen underwent histochemical stain with hematoxylin-eosin (H&E), immunohistochemically stained with major histocompatibility complex class I (MHC-I) and MHC-II, complement membrane attack complex (MAC), and picrosirius red stained [21]. Regarding the diagnosis of fibrosing myopathy, picrosirius red polarized images were digitally captured by an optical microscope with a polarizing filter at a magnification of 200 X and an image size of 1600x1200 pixels into red green blue (RGB) 24 bits TIFF (Tagged Image File Format) files. The collagen fibers in the fibrous tissue appeared as a bright red color. Muscle biopsies were reviewed and then the muscle pathology was classified by an experience muscle pathologist (S.S.).

2.5. Definition of Pathological Muscle Biopsy Subgroup

Muscle pathological findings were classified as the followings**:***(i) Polymyositis (PM)* - the presence of endomysial

inflammatory cell infiltration which is surrounding or invading non-necrotic fibers [22]; *(ii) Dermatomyositis (DM)* - presence of perifascicular atrophy [22]; (iii) *Inclusion body myositis (IBM)* - presence of endomysial inflammatory cell infiltration and rimmed vacuoles [23]; *(iv) Immune-mediated necrotizing myopathy (IMNM)* - presence of scattered necrotic and regenerating muscle fibers, sparse inflammation and presence of sarcolemma immunohistochemically staining for MAC [24]; *(v) Non-specific myositis (NsM)*- presence of scattered perivascular, perimysium or endomysial inflammatory infiltration that does not fulfill to the definition of PM, DM, or IMNM [22]; and (vi) *Fibrosing myopathy (FM)* - presence of predominantly fibrosis without fulfilled pathological changes of the above-mentioned myopathies [9, 10].

2.6. Statistical Analysis

The descriptive data are presented as frequency (percentage: %), mean ± standard deviation (SD), or median (interquartile range 1, 3: IQR 1, 3). Three subgroups of muscle pathologic findings in this study included SSc-IMNM, NsM, and PM. Therefore, a comparison of categorical variables among the three subgroups was analyzed using Fisher's exact test. Continuous variables between the three subgroups were compared using the Kruskal-Wallis test or the one-way ANOVA test. p-values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA).

3. RESULTS

3.1. Clinical Characteristics of the Total SSc-M

A total of 23 SSc-M patients that fulfilled the inclusion criteria (14 female [60.9%], 19 DcSSc [82.6%], 17 anti-topoisomerases I antibody-positive [73.9%]) had a mean ± SD age of 53.6 ± 7.7 years; median (IQR 1, 3) duration of SSc and myopathy was 11 (4, 14) months and 2 (0, 3) months, respectively. There were no patients with anti-centromere antibody-positive in our study population. At the biopsy date, their mean ± SD mRSS was 23 ± 15.3, CK levels were 2442.8 ± 1431.2 U/L (median: 2425.0 U/L [1567.0, 3368.0]) and ESR levels were 72.8 ± 34.2 mm/hr. There were 17 (73.9%) SSc-M patients with mild to moderate weakness and 6 (26.1%) with severe weakness. There were six patients (26.1%) with the digital ulcer, 15 (65.2%) with arthritis, 4 (17.4%) with tendon friction rub, 17 (73.9%) with dysphagia, 13 (56.5%) with GERD, 16 (69.6%) ILD, 6 (26.1%) suspected PH, and 4 (17.4%) CHF. Out of 15 patients with clinical arthritis, two (13.3%) have rheumatoid factor positive-low liter. Out of the 23 muscle histological findings after undergoing the staining methods, 14 (60.8%) patients had IMNM, 6 (26.1%) NsM, and 3 (13%) PM. There were no FM, IBM, and DM in our population. The patients were then divided into three subgroups: (i) IMNM, (ii) NsM, and (iii) PM.

3.2. Comparison of Clinical Manifestations, and Laboratory Findings among SSc-INAM, NsM, and PM

The comparative analysis of the baseline clinical characteristics and laboratory findings among the three inflammatory patterns is shown in Table **1**. Regarding the demographic data, the IMNM subgroup tended to have more prevalence of female gender and had longer disease duration of SSc than the others. Whereas, the NsM subgroup tended to have a higher proportion of DcSSc subtype, anti-topoisomerase-I antibody-positive and shorter time from muscle weakness symptoms to muscle biopsy than the other group. Regarding organ involvement, a higher prevalence of severe muscle weakness and arthritis was observed in the IMNM subgroups. There were no statistical differences in other clinical manifestations, including digital ulcer, tendon friction rub, dysphagia, GERD, ILD, suspected PH, and CHF. No scleroderma renal crisis was observed in our population. In addition, mean or median baseline laboratory values, including CK level, ESR, Hb, and Cr, as well as current medical treatment (data not shown), showed no statistically significant within the three inflammatory patterns.

Table 1. Demographics, clinical features and laboratory findings comparing SSc-IMNM, NsM, and PM.

Variables	INAM (n= 14)	NsM (n=6)	PM (n=3)	*p*-value
Demographic				
Female [a]	11 (78.6)	2 (33.3)	1 (33.3)	0.112
DcSSc subtype [a]	11 (78.6)	6 (100.0)	2 (66.7)	0.414
Anti-topoisomerase I-positive [a]	10 (71.4)	6 (100.0)	1 (33.3)	0.100
Age, years [c]	54.3 ± 6.6	55.2 ± 9.3	47.3 ± 9.1	0.325
SSc duration, months [b]	12 (6, 25)	6 (3.7, 11)	3[†]	0.153
Myopathy duration, months [b]	2 (0, 5)	0.5 (0, 2.2)	3[†]	0.233
Organ involvement				
Proximal muscle strength [c]	3.4 ± 0.8	3.8 ± 0.4	4 ± 0	0.175
Mild-mod weakness [a]	8 (57.1)	6 (100.0)	3 (100.0)	1.00
Severe weakness [a]	6 (42.9)	0	0	NA
Myalgia [a]	8 (57.1)	3 (50.0)	3 (100.0)	0.502
mRSS [b]	23.9 ± 16.2	26.5 ± 14.6	8.0 ± 4.2	0.381
Hypo-hyperpigmentation [a]	9 (64.3)	5 (83.3)	3 (100.0)	0.511
Digital ulcer [a]	4 (28.6)	2 (33.3)	0	0.659

(Table 1) contd.....

Variables	INAM (n= 14)	NsM (n=6)	PM (n=3)	*p*-value
Arthritis [a]	12 (85.7)	3 (50.0)	0	0.008**
Tendon friction rubs [a]	3 (21.4)	1 (16.7)	0	1.00
Dysphagia [a]	8 (57.1)	6 (100.0)	3 (100.0)	1.00
Gastroesophageal reflux [a]	8 (57.1)	4 (66.7)	1 (33.3)	0.708
Interstitial lung disease [a]	11 (78.6)	3 (50.0)	2 (66.7)	0.547
Suspected pulmonary hypertension [a]	4 (28.6)	0	2 (66.7)	1.00
Congestive heart failure [a]	3 (21.4)	1 (16.7)	0	1.00
Lab findings				
Creatine kinase, U/L [b]	2432.0 (1588.0, 3513.2)	2176.0 (1046.0, 3916.2)	1998.7± 550.3	0.932
ESR, mm/hr. [b]	73.5 ± 40.7	67.2 ± 26.5	79.0 ± 12.8	0.780
Hemoglobin, g/L [c]	10.9 ± 2.1	11.1 ± 1.3	12.9 ± 0.8	0.258
Creatinine, mg/dl [c]	0.8 ± 0.3	0.9 ± 0.3	0.7 ± 0.2	0.742

Note: Data shown are number (%), mean ± SD, median (IQR 1,3), † median.

Abbreviations: IMNM, immune-mediated necrotizing myopathy; NsM, nonspecific myopathy; PM, polymyositis; DcSSc, Diffuse cutaneous SSc; mRSS, modified Rodnan skin score; ESR, erythrocyte sedimentation rate. [a] Fisher's exact test, [b] Kruskal-Wallis test, [c] one-way ANOVA test. ** $p < 0.01$.

4. DISCUSSION

In this small retrospective study of Thai patients diagnosed with systemic sclerosis-associated myopathy (SSc-M), we have seen only inflammatory patterns comprising IMNM, NsM, and PM; no fibrosing myopathy patterns were observed. Furthermore, we have found that IMNM tended to have more severe muscle weakness and higher prevalence of arthritis than the other inflammatory patterns.

Our SSc-M had predominantly female gender (60.9%) with DcSSc subtype (82.6%) similar to those populations in the study of Paik *et al*. [10] and Matas-García *et al*. [13], which their proportion of female and DcSSc subtype ranged from 70-75%. In contrast to the prior studies [10, 13], our patients had a slightly shorter disease duration of SSc from the first NRP (1 year *vs*. 2 years) and a slightly longer period from muscle weakness to muscle biopsy (2 months *vs*. 0.5 months). In addition, prior studies [10, 13] reported that their SSc-M comprised both fibrosing myopathy and inflammatory myopathy comprising NsM, IMNM, PM, and DM differed from our populations that had only inflammatory myopathies pattern.

Paik *et al*. [10] and Matas-García *et al*. [13] reported that SSc patients with fibrosing myopathy presented a higher prevalence of myocardial disease, conduction abnormalities or arrhythmias, DcSSc subtype, anti-topoisomerase I-antibodies, and had higher mortality compared to SSc with inflammatory myopathies. Ranque *et al*. pointed out that histological muscle inflammation, not fibrosing myopathy, was associated with a good response to corticosteroids. Still, the correlation between muscle pathology and clinical presentation was inconclusive [5, 6]. However, to our knowledge, there has been scant published data regarding the comparison of clinical presentation within the different subgroups of inflammatory myopathies pattern.

In this study, we would like to point out that the clinical presentation within the different subgroups of inflammatory patterns shows some dissimilar. Our SSc with IMNM showed a more severe clinical presentation, including more severe muscle weakness and arthritis, than the NsM and PM group at the time of diagnosis. However, no significant difference among the three inflammatory patterns regarding other organ complications as well as CK and ESR levels. Further larger comparative studies between different subgroups within an inflammatory pattern of SSc-M regarding clinico-biochemical characteristic and long-term treatment outcome is needed.

As a retrospective study, this study has several limitations. The small number of muscle pathology specimens for reviewing is a major limitation, which might affect the power of statistical analysis. Also, there is no global standard definition of SSc-M, this leads to the use of this study's definition based on the presence of muscle weakness, elevated CK, and presence of myopathy from a muscle biopsy. In addition, clinical data were recorded and investigation for organ involvement was investigated routinely depending on their attending rheumatologists. Therefore, the assessment of organ involvement might have some bias. Another limitation is that muscle pathology findings and classification were reviewed by one experienced muscle pathologist. Finally, myositis-specific antibodies or myositis-associated antibodies were not available in our institution during the study period; hence, serological information among the subgroups is lacking.

CONCLUSION

In this study, we found that pathological findings of Thai patients with SSc-M were IMNM, NsM, and PM, of which the majority were IMNM. No fibrosing myopathy was observed in Thai SSc-M. SSc-IMNN tended to have more severe muscle weakness and higher proportion of arthritis at initial presentation than the other inflammatory patterns. A larger prospective study comparing clinico-biochemical features within different inflammatory patterns is essential to confirm our findings.

AUTHORS' CONTRIBUTION

All authors fulfilled the authorship criteria established by the International Committee of Medical Journak Editors (ICMJE). Songkiet Suwansirikul: study design, muscle pathology reviewing, data analysis, and writing manuscript; Suparaporn Wangkaew: study design, data collection, data validation, analysis, and writing manuscript; Jirapath intum:

data collection; Chontichaporn Tejamai: muscle biopsy specimen preparation. All authors reviewed and approved the final manuscript version submitted for publication.

LIST OF ABBREVIATIONS

CHF	=	Congestive Heart Failure
CK	=	Creatine Kinase
Cr	=	Creatinine
DcSSc	=	Diffuse Cutaneous Ssc
DM	=	Dermatomyositis
ESR	=	Erythrocyte Sedimentation Rate
FM	=	Fibrosing Myopathy
GERD	=	Gastroesophageal Reflux Disease
H&E	=	Hematoxylin-Eosin
IBM	=	Inclusion Body Myositis
ILD	=	Interstitial Lung Disease
IMNM	=	Immune-Mediated Necrotizing Myopathy
LcSSc	=	Limited Cutaneous Ssc
MAC	=	Membrane Attack Complex
MHC-I	=	Major Histocompatibility Complex Class I
mRSS	=	Modified Rodnan Skin Score
NRP	=	Non-Raynaud's Phenomenon
NsM	=	Non-Specific Myositis
PH	=	Suspected Pulmonary Hypertension
PM	=	Polymyositis
RGB	=	Red Green Blue
SD	=	Standard Deviation
SRC	=	Scleroderma Renal Crisis
SSc	=	Systemic Sclerosis
SSc-M	=	Systemic Sclerosis-Associated Myopathy

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study was approved by the Research Ethics Committee of Chiang Mai University (study code: Med-2562-06857).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

I confirm that the study was carried out following relevant guidelines and regulations.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

Data and materials are available upon request to the corresponding author [S.W].

FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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Declared none.

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