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

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Abstract:
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 myopathy (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.

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].
The diagnosis of SSc-M 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 under a microscope with a polarizing filter at a magnification of 200 X.

2.5. Definition of Pathological Muscle Biopsy Subgroup

Muscle pathological findings were classified as the following: (i) Polymyositis (PM) - the presence of endomysial 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 tests 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].

2.2. 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-
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 endomyosial 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 endomyosial 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 DeSSc [82.6%], 17 anti-topoisomerase-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 DeSSc subtype, anti-topoisomerase-I antibody-positive and shorter time from 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.

<table>
<thead>
<tr>
<th>Variables</th>
<th>INAM (n=14)</th>
<th>NsM (n=6)</th>
<th>PM (n=3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female †</td>
<td>11 (78.6)</td>
<td>2 (33.3)</td>
<td>1 (33.3)</td>
<td>0.112</td>
</tr>
<tr>
<td>DeSSc subtype †</td>
<td>11 (78.6)</td>
<td>6 (100.0)</td>
<td>2 (66.7)</td>
<td>0.414</td>
</tr>
<tr>
<td>Anti-topoisomerase-I-positive †</td>
<td>10 (71.4)</td>
<td>6 (100.0)</td>
<td>1 (33.3)</td>
<td>0.100</td>
</tr>
<tr>
<td>Age, years †</td>
<td>54.3 ± 6.6</td>
<td>55.2 ± 9.3</td>
<td>47.3 ± 9.1</td>
<td>0.325</td>
</tr>
<tr>
<td>SSc duration, months †</td>
<td>12 (6, 25)</td>
<td>6 (3.7, 11)</td>
<td>3 †</td>
<td>0.153</td>
</tr>
<tr>
<td>Myopathy duration, months †</td>
<td>2 (0, 5)</td>
<td>0.5 (0, 2.2)</td>
<td>3 †</td>
<td>0.233</td>
</tr>
</tbody>
</table>

| **Organ involvement** |             |           |          |         |
| Proximal muscle strength † | 3.4 ± 0.8 | 3.8 ± 4.0 | 4 ± 0 | 0.175   |
| Mild-mod weakness † | 8 (57.1) | 6 (100.0) | 3 (100.0) | 1.00   |
| Severe weakness † | 6 (42.9) | 0 | 0 | NA |
| Myalgia † | 8 (57.1) | 3 (50.0) | 3 (100.0) | 0.502   |
| nRSS † | 23.9 ± 16.2 | 26.5 ± 14.6 | 8.0 ± 4.2 | 0.381   |
| Hypo-hyperpigmentation † | 9 (64.3) | 5 (83.3) | 3 (100.0) | 0.511   |
| Digital ulcer † | 4 (28.6) | 2 (33.3) | 0 | 0.659   |
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-Garcia 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-Garcia et al. [13] reported that SSc patients with fibrosing myopathy presented a higher prevalence of myocardial disease, conduction abnormalities or arrhythmias, DeSSc 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 Journal 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; Jiraphat 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  
DeSSc = 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  
LeSSc = 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  
SSe = 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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