Recognising the spectrum of scleromyositis: HEp-2 ANA patterns allow identification of a novel clinical subset with anti-SMN autoantibodies

Océane Landon-Cardinal,1 Alexandra Baril-Dionne,1 Sabrina Hoa,1 Alain Meyer,2 Valérie Leclair,3 Josiane Bourré-Tessier,1 Anne-Marie Mansour,4 Farah Zarka,4 Jean-Paul Makhzoum,4 Jessica Nehme,5 Eric Rich,1 Jean-Richard Goulet,1 Tamara Grodzicky,1 Martial Koenig,6 France Joyal,6 Isabelle Richard,7 Marie Hudson,3,8 Ira Targoff,9 Minoru Satoh,10 Marvin J Fritzler,11 Jean-Alain Meyer12

ABSTRACT

Objective To describe systemic sclerosis (SSc) with myopathy in patients without classic SSc-specific and SSc-overlap autoantibodies (aAbs), referred to as seronegative scleromyositis.

Methods Twenty patients with seronegative scleromyositis diagnosed by expert opinion were analysed retrospectively for SSc features at myositis diagnosis and follow-up, and stratified based on HEp-2 nuclear patterns by indirect immunofluorescence (IIF) according to International Consensus of Autoantibody Patterns.

Results A nuclear dot HEp-2 IIF pattern is associated with interstitial lung disease (ILD) and renal crisis. Second, a speckled pattern uncovered multiple rare SSc-specific aAbs. Third, the nuclear dots pattern was associated with aAbs to survival of motor neuron (SMN) complex and a novel scleromyositis subset characterized by calcinosis but infrequent ILD and renal crisis.

Conclusions SSc skin involvement is often absent in early seronegative scleromyositis. A nuclear dot HEp-2 IIF pattern is associated with anti-SMN autoantibodies and a novel scleromyositis subset.

Key messages

What is already known about this subject?

► Scleromyositis is an emerging, yet poorly characterised, subset of myositis associated with features of systemic sclerosis.

What does this study add?

► SSc skin involvement is often absent in early seronegative scleromyositis.

► A nuclear dot HEp-2 IIF pattern is associated with anti-SMN autoantibodies and a novel scleromyositis subset.

How might this impact on clinical practice?

► ANA positivity, Raynaud phenomenon, SSc-type capillaroscopy and/or lower oesophageal dysmotility are clues for early seronegative scleromyositis identification.

► HEp-2 IIF patterns allow novel clinical scleromyositis subsets to emerge.

INTRODUCTION

Meeting the classification criteria of both systemic sclerosis (SSc) and myositis has been proposed as a definition of an SSc-myositis overlap syndrome.1–3 In the elaboration of the 2013 American College of Rheumatology (ACR)/EULAR SSc classification criteria, myositis was not selected as an SSc feature and instead was considered an SSc mimicker.4 Nevertheless, myositis has been reported with varying frequency in all serological subsets of SSc.5–8 Defining muscle involvement in SSc as scleromyositis9 puts emphasis on the concept that SSc may also present as a myositis with only mild SSc features.
Classic SSc-specific autoantibodies (aAbs) include anticientromere, -topoisomerase I, -RNA polymerase III, -Th/To and -U3RNP, whereas SSc-overlap aAbs include anti-U1RNP, -PM-Scl and -Ku. These aAbs are associated with fluorescent antinuclear antibody (ANA) patterns by indirect immunofluorescence (IIF) assay using the International Consensus of Autoantibody Patterns (ICAP) classification. In contrast, scleromyositis without classic SSc-specific or SSc-overlap aAbs has not been thoroughly described. This serological subset consists of several rare aAbs associated with nuclear and cytoplasmic fluorescent patterns, including anti-RuvBL1/2, anti-U4/U6RNP, anti-U5RNP, anti-U11/12RNP aAbs, as well as yet to be identified novel aAbs.

The objective of this study was to describe the clinic-serosological features of 20 patients with seronegative scleromyositis, that is, with no classic SSc-specific and SSc-overlap aAbs. Patient characteristics were analysed for the presence of ACR/EULAR myositis, SSc criteria and any non-ACR/EULAR SSc features. Serology was defined as previously published. ANAs were determined by IIF on HEp-2 cells and the threshold value for positivity was >1:160. An anti-ENA panel was used to detect aAbs to centromere protein B, topoisomerase I and U1RNP. A commercial line blot assay (Myositis Profile 3 or 4, Euroimmun AG, Luebeck, Germany) was used to detect SSc-overlap anti-PM-Scl and anti-Ku aAbs.

Serology
Baseline immunological studies were performed at CHUM and HSCM as previously described. ANAs were determined by IIF on HEp-2 substrate (Inova Diagnostics, San Diego, CA, USA) and read by technologists with >15 years of experience. HEP-2 IIF patterns were classified according to the ICAP standardised nomenclature (www.anapat.org). Anti-centromere aAbs were identified based on a discrete speckled nuclear pattern (AC-3). aAbs against centromere autoantigens CENP-A and CENP-B, topoisomerase I, RNA polymerase III (RP11 and RP155), PM-Scl (PM75 and PM100), Ro52/TRIM21, PDGFR, Ku, Th/To, NOR90/hUBF and U3RNP (fibrillarin) were detected by an SSc profile line immunoblot assay (Euroimmun AG). Overall, classic SSc-specific aAbs detected included aAbs to centromere proteins, topoisomerase I, RNA polymerase III, Th/To and U3RNP (fibrillarin) whereas SSc-overlap aAbs included aAbs to U1RNP, PM-Scl (75 and 100) and Ku. In the presence of unexplained nucleolar IIF pattern, testing for anti-Th/To aAbs was also done, as previously described.

All available sera were analysed for aAbs by protein–assisted immunoprecipitation using HeLa cell extracts, both for nucleic acid analysis (RNA silver stain) and for proteins (metabolically labelled with 35S-methionine) as described. aAbs to survival of motor neuron (SMN) /geminin complex were tested in sera from 19 of the 20 patients by immunoprecipitation of 35S-methionine metabolically labelled K562 cell extracts as described.

METHODS
Patients
We conducted a retrospective study of 20 patients with seronegative SSc with a diagnosis of scleromyositis and without SSc-specific and SSc-overlap aAbs. Given the current absence of a gold standard for the definition of scleromyositis, this diagnosis was made by expert opinion (consensus of ≥2 experts). These patients were identified in a cohort of 340 patients with autoimmune myositis (AIM) at the Centre Hospitalier de l’Université de Montréal (CHUM) and Hôpital du Sacré-Coeur de Montréal (HSCM) (Montréal, Québec, Canada) recruited between 1967 and 2019, as previously described.

Study variables
A retrospective medical record review using a standardised protocol was performed to collect clinical data, laboratory and imaging investigations, and muscle biopsy findings, as described previously in detail. Objective oropharyngeal dysphagia was defined by an abnormal videofluoroscopic swallowing study and/or the need for percutaneous gastrojejunostomy. Presence of lower oesophageal dysmotility was defined by either manometry or evidence on chest CT of lower oesophageal dilatation. Axial myopathy was characterised by weakness of the paraspinal muscles with head drop and/or camptocormia as prominent clinical features. Perimysial, perivascular or endomysial inflammation, and evidence of perifascicular atrophy, rimmed vacuoles and capillary abnormalities in muscle biopsies were recorded. Abnormal SSc-type capillary microscopy was defined as previously published.

Inspired by the sequential occurrence of lung, muscle and joint manifestations in the time course of antisynthetase syndrome, we subclassified scleromyositis patients in four subsets according to their presenting feature at myositis diagnosis:

1. Patients meeting the 2013 ACR/EULAR SSc classification criteria were referred to as having a definite SSc phenotype at myositis diagnosis.
2. For patients not meeting the SSc classification criteria, the presenting SSc features could either be
   a. Raynaud phenomenon, as implied by the concept of very early diagnosis of SSc;
   b. Interstitial lung disease (ILD), as epitomised by ILD with anti-Th/To SSc aAbs;
   c. Isolated muscle involvement with neither Raynaud phenomenon nor ILD, as suggested by SSc-specific muscle histopathology.

and were also tested by addressable laser bead immunoas-
say (ALBIA) for additional corroboration using purified,
full-length, recombinant human SMN protein (Enzo Bio-
chem, Farmingdale, New York, USA) with methods as
previously described and results expressed as median
fluorescence units (MFU) with positivity defined as 3 SD
above the mean of normal and unrelated disease controls
(>900 MFU). Using line blot assay and protein A-assisted
immunoprecipitation, none of the 20 patients had aAbs
to synthetases.

### Statistical analysis

Descriptive statistics were used to describe the cohort. Comparisons among subsets were made using χ² analysis,
Fisher two-tailed exact test, where applicable, or the
Mann-Whitney U test. Kaplan-Meier curves were con-
structed to estimate 1-year, 5-year and 10-year survivals
of the cohort.

### Ethic statements

The study was approved by the CHUM (reference num-
ber 2015–5607-CE14.238) and HSCM (2014–1042) ethics
committees.

### RESULTS

#### Identifying 20 patients with seronegative scleromyositis, that is, with no classic SSc-specific and SSc-overlap aAbs

A diagnosis of scleromyositis was made by expert opinion
in 86 of 340 patients with AIM of our cohort (figure 1),
consisting of 19 patients with classic SSc-specific aAbs, 47
patients with SSc-overlap aAbs and 20 patients without
classic SSc-specific and SSc-overlap aAbs. The latter
group is referred to herein as seronegative scleromyositis
and is the focus of this report. This group of patients
included 3 men and 17 women, with a median age of
49.7 years (range 24.6–69 years) and a median follow-up
of 6.5 years (range 3 months–32 years). One-year, 5-year
and 10-year survivals were 90.0%, 78.5% and 56.6%,
respectively. Cancer within 3 years of diagnosing myositis
was identified in only one patient.

#### Myopathic features in 20 patients with seronegative scleromyositis at myositis diagnosis

Proximal muscle weakness was documented in most
patients (90%). Interestingly, one patient (patient 6,
table 1) displayed a predominantly axial myopathy
(camptocormia). Three patients (15%) presented with
objective oropharyngeal dysphagia. Serum creatine
kinase (CK) was elevated in all patients, with a median
value of 1754 IU/L (range 300–12 410 IU/L). Myopathic
electromyography (EMG) was observed in all 17 tested
patients. Muscle biopsy was performed in all but two
patients, and inflammation was documented in seven
patients (perimysial and/or perivascular lymphocytic
infiltrates in six patients and endomysial in one patient).

Only 10 patients (50%) met the 2017 EULAR/ACR idio-
pathic inflammatory myopathy (IIM) classification cri-
teria at myositis diagnosis. Probability of having IIM
according to these criteria was (1) definite IIM in 10% (n=2/20), (2) probable IIM in 40% (n=8/20), (3) possi-
ble IIM in 0% and (4) not classifiable as IIM in 50%
(n=10/20).

#### SSc features in 20 patients with seronegative scleromyositis at myositis diagnosis

At myositis diagnosis, only 11 patients (55%) met the
2013 ACR/EULAR SSc classification criteria (table 1).
Definite SSc was therefore the presenting phenotype in
these patients (n=11). Limited SSc skin involvement was
observed in nine of them (82%). New-onset Raynaud
phenomenon in the previous year was seen in 7 of these
11 patients (64%), whereas myositis was the first non-
Raynaud SSc manifestation in 3 of them (27%).

In the remaining patients (n=9/20) not fulfilling the
2013 ACR/EULAR SSc classification criteria, the present-
ing SSc features were either Raynaud phenomenon
(n=5), ILD (n=1) or isolated SSc muscle involvement
(n=3), respectively. All these patients presented without
SSc skin involvement, that is, sine scleroderma, although
three patients displayed telangiectasias and/or puffy fin-
gers (table 1). Myositis was the most common first non-
Raynaud SSc manifestation (55%), especially in patients
presenting as sine scleroderma (n=8/9).

Taken together, SSc sine scleroderma (n=9/20, 45%)
and limited cutaneous SSc (n=9/20, 45%) were the domi-
nant subsets of SSc at myositis diagnosis, while diffuse
cutaneous SSc (n=2, 10%) was less frequent. Interest-
ingly, lower oesophageal dysmotility was present in 10 of

---

**Figure 1** Identification of seronegative scleromyositis by
expert opinion in an autoimmune myositis cohort.
Table 1  SSc features at myositis diagnosis in 20 patients with seronegative scleromyositis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>SSc skin involvement</th>
<th>ILD</th>
<th>Raynaud</th>
<th>Abnormal NFC</th>
<th>First non-Raynaud SSc symptom</th>
<th>Lower oesophageal dysmotility</th>
<th>Laboratory</th>
<th>Classification criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diffuse</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Puffy fingers</td>
<td>Y</td>
<td>AC5 1:1280</td>
<td>2139 N (38%) Y</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Puffy fingers</td>
<td>Y</td>
<td>AC4 1:640</td>
<td>6680 Y (79%) Y</td>
</tr>
<tr>
<td>3</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Trig. neuropathy</td>
<td>ND</td>
<td>AC6/7 1:5120</td>
<td>2564 N (38%) Y</td>
</tr>
<tr>
<td>4</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Myositis</td>
<td>Y</td>
<td>AC6/7 1:1280</td>
<td>3675 N (13%) Y</td>
</tr>
<tr>
<td>5</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Puffy fingers</td>
<td>Y</td>
<td>N</td>
<td>385 N (23%) Y</td>
</tr>
<tr>
<td>6</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>ND</td>
<td>Sclerodactyly</td>
<td>ND</td>
<td>AC8 1:1280</td>
<td>656 N (38%) Y</td>
</tr>
<tr>
<td>7</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>GERD</td>
<td>Y</td>
<td>N</td>
<td>546 N (38%) Y</td>
</tr>
<tr>
<td>8</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Sclerodactyly</td>
<td>ND</td>
<td>AC6/7 1:1280</td>
<td>2974 N (3%) Y</td>
</tr>
<tr>
<td>9</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Sclerodactyly</td>
<td>Y</td>
<td>N</td>
<td>358 Y (85%) Y</td>
</tr>
<tr>
<td>10</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Dyspnea</td>
<td>Y</td>
<td>N</td>
<td>880 N (5%) Y</td>
</tr>
<tr>
<td>11</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Myositis</td>
<td>ND</td>
<td>AC1 1:1280</td>
<td>1743 N (5%) Y</td>
</tr>
<tr>
<td>12</td>
<td>Sine</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Myositis</td>
<td>N</td>
<td>N</td>
<td>300 Y (77%) N</td>
</tr>
<tr>
<td>13</td>
<td>Sine</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Myositis</td>
<td>Y</td>
<td>AC6/7 1:1280</td>
<td>1494 Y (89%) N</td>
</tr>
<tr>
<td>14</td>
<td>Sine</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>GERD</td>
<td>Y</td>
<td>AC6/7 1:640</td>
<td>1738 Y (67%) N</td>
</tr>
<tr>
<td>15</td>
<td>Sine</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Myositis</td>
<td>Y</td>
<td>N</td>
<td>1765 Y (89%) N</td>
</tr>
<tr>
<td>16</td>
<td>Sine</td>
<td>N</td>
<td>Y</td>
<td>ND</td>
<td>Myositis</td>
<td>ND</td>
<td>AC4 or AC5 1:2560</td>
<td>1536 Y (75%) N</td>
</tr>
<tr>
<td>17</td>
<td>Sine</td>
<td>Y</td>
<td>N</td>
<td>ND</td>
<td>Myositis</td>
<td>ND</td>
<td>AC6/7 1:1280</td>
<td>6000 N (38%) N</td>
</tr>
<tr>
<td>18</td>
<td>Sine</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Myositis</td>
<td>ND</td>
<td>AC4 1:1280</td>
<td>9329 Y (75%) N</td>
</tr>
<tr>
<td>19</td>
<td>Sine</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Myositis</td>
<td>ND</td>
<td>N</td>
<td>12 410 Y (90%) N</td>
</tr>
<tr>
<td>20</td>
<td>Sine</td>
<td>N</td>
<td>N</td>
<td>ND</td>
<td>Myositis</td>
<td>ND</td>
<td>AC5 ND</td>
<td>2000 Y (91%) N</td>
</tr>
<tr>
<td>Total</td>
<td>Sine, 45%</td>
<td>30%</td>
<td>75%</td>
<td>73%, n=11/15</td>
<td>Myositis, 55%</td>
<td>91%, n=10/11</td>
<td>ANA+, 65%</td>
<td>Median CK, 1754 50% 55%</td>
</tr>
</tbody>
</table>

*This patient had an axial myopathy.

ACR, American College of Rheumatology; ANA, antinuclear antibody; CK, creatine kinase; GERD, gastro-oesophageal reflux disease; ICAP, International Consensus on Antinuclear Antibody Patterns; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; N, no; ND, no data; NFC, nailfold capillaroscopy; ; sine, sine scleroderma; SSc, systemic sclerosis; Trig., trigeminal; Y, yes.
11 (91%) investigated patients, supporting an early diagnosis of SSc. Additionally, two-thirds (n=13/20) of patients with seronegative scleromyositis without classic SSC-specific and SSC-overlap aAbs had a positive HEp-2 IIF nuclear pattern (all with titers ≥1/320) (table 1).

Most patients with seronegative scleromyositis met the ACR/EULAR classification criteria for SSc at last follow-up

With the benefit of a median follow-up of 6.7 years (range 0.3–32 years), 80% (n=16/20) of patients with seronegative scleromyositis ultimately met the 2013 ACR/EULAR SSc classification criteria (table 1). In contrast, at last follow-up, 40% (n=8/20) of the patients were included in a recent clinico-sero-pathological study. Of note, anti-SMN is typically associated with the few nuclear dots pattern (AC-7 pattern characterised by 1–6 dots) as shown in figure 3. However, not all sera had a clear-cut AC-7 pattern because some had >6 pleomorphic dots/nucleus than would be seen with classical AC-7. This may be explained by the presence of unidentified antigenic targets that give both an AC-6 and AC-7 pattern, as these sera were not monospecific when analysed (see figure 3). The phenotype of patients with anti-SMN aAbs is shown in table 3. At diagnosis, three patients had limited cutaneous SSc, whereas two patients had SSC sine scleroderma. At last follow-up, four patients had limited SSc and a single patient had diffuse SSc. All patients were female with proximal weakness, displayed elevated serum CK levels (range 1494–3675 IU/L) and had an abnormal EMG. Arthritis and SSC calcinosis were each seen in three patients (60%), while digital ulcers, ILD, bilateral trigeminal neuropathy and small-bowel involvement with pneumatosis and retropneumoperitoneum were each seen in individual patients. No scleroderma renal crisis was observed at follow-up. Remarkably, one patient (patient 3, table 3) had three siblings suffering from spinal muscular atrophy.

Other HEp-2 IIF patterns: one patient had a nucleolar pattern (AC-8), while another patient had a homogeneous pattern (AC-1).

DISCUSSION

There is a paucity of evidence on scleromyositis without classic SSC-specific and SSC-overlap aAbs. Only 10 such patients were included in a recent clinico-sero-pathological...
Table 2  SSc features at last follow-up in 20 patients with seronegative scleromyositis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>SSc skin involvement</th>
<th>ILD</th>
<th>Raynaud</th>
<th>Abnormal NFC</th>
<th>Lower oesophageal dysmotility</th>
<th>Isolated DLCO ≤ 70%</th>
<th>SRC</th>
<th>Non ACR/EULAR SSc autoantibodies</th>
<th>Classification criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EULAR/ACR IIM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ACR/EULAR SSc</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Follow-up duration, years</td>
</tr>
<tr>
<td>1</td>
<td>Diffuse</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Anti-U4/U6RNP</td>
<td>N Y 1.9</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Anti-RuvBL1/2</td>
<td>Y Y 9.5</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td>Anti-SMN</td>
<td>N Y 6.5</td>
</tr>
<tr>
<td>4</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Anti-SMN</td>
<td>N Y 5</td>
</tr>
<tr>
<td>5</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td></td>
<td>Y Y 0.3</td>
</tr>
<tr>
<td>6</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td></td>
<td>N Y 0.3</td>
</tr>
<tr>
<td>7</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td></td>
<td>N Y 9.5</td>
</tr>
<tr>
<td>8</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td>Anti-SMN</td>
<td>Y Y 4.5</td>
</tr>
<tr>
<td>9</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td></td>
<td>Y Y 7</td>
</tr>
<tr>
<td>10</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td></td>
<td>N Y 3</td>
</tr>
<tr>
<td>11</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td></td>
<td>N Y 3.5</td>
</tr>
<tr>
<td>12</td>
<td>Sine</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td>Y N 18</td>
</tr>
<tr>
<td>13</td>
<td>Limited</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Anti-SMN</td>
<td>Y Y 29</td>
</tr>
<tr>
<td>14</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Anti-SMN</td>
<td>Y Y 22</td>
</tr>
<tr>
<td>15</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td></td>
<td>Y Y 21</td>
</tr>
<tr>
<td>16</td>
<td>Sine</td>
<td>N</td>
<td>Y</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td></td>
<td>Y N 8</td>
</tr>
<tr>
<td>17</td>
<td>Limited</td>
<td>Y</td>
<td>Y</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N Y 32</td>
</tr>
<tr>
<td>18</td>
<td>Limited</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>ND</td>
<td>Y</td>
<td>N</td>
<td>Anti-RuvBL1/2</td>
<td>Y N 3</td>
</tr>
<tr>
<td>19</td>
<td>Diffuse</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td></td>
<td>Y Y 6</td>
</tr>
<tr>
<td>20</td>
<td>Sine</td>
<td>N</td>
<td>Y</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td>Anti-U5RNP</td>
<td>Y N 13.5</td>
</tr>
<tr>
<td>Total</td>
<td>Limited, 80%</td>
<td>45%</td>
<td>95%</td>
<td>69%, n=11/16</td>
<td>93%, n=13/14</td>
<td>12%, n=2/17</td>
<td>15%</td>
<td>45%</td>
<td>60% 80% Mean duration 6.8</td>
</tr>
</tbody>
</table>

ACR, American College of Rheumatology; DLCO, diffusing capacity of lung for carbon monoxide; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; NFC, nailfold capillaroscopy; N, no; ND, no data; NFC, nailfold capillaroscopy; sine, sine scleroderma; SMN, survival of motor neuron; SRC, scleroderma renal crisis; SSc, systemic sclerosis; Y, yes.
study of 37 patients with scleromyositis. In the present study, we describe in-depth 20 patients with seronegative scleromyositis that were identified from a cohort of 340 carefully phenotyped patients with AIM.\textsuperscript{16–18}

SSc skin involvement is often absent in early scleromyositis
Knowledge of SSc features included in the 2013 ACR/EULAR SSc classification criteria is a step towards the early identification of SSc in patients with suspected AIM. However, these criteria put emphasis on the presence of SSc skin involvement, yet this feature was initially absent in almost half (45%) of our scleromyositis patients. The present study therefore explores serological, myological and non ACR/EULAR SSc features that led to an early diagnosis of scleromyositis by expert opinion.

Current definitions of scleromyositis are insensitive
In the absence of a gold standard defining scleromyositis, meeting the classification criteria of both IIM and SSc is often used in practice. However, defining scleromyositis as the fulfillment of these classification criteria lacks sensitivity, as only two patients (10%) in this study met this definition at myositis diagnosis. Interestingly, myositis was the first non-Raynaud manifestation of SSc in 11 patients (55%), also making the case for clinicians to recognise myositis as a potential feature of early SSc.

SSc sine scleroderma as a clue to early identification of scleromyositis in seronegative patients
Only 55% of our patients presented SSc skin involvement at myositis diagnosis, and the remaining patients presented with SSc sine scleroderma. Interestingly, most of them (89%) presented, singly or in combination, high titer HEP-2 IIF positivity, new onset Raynaud phenomenon, SSc-type capillaroscopy and/or lower oesophageal dysmotility, which are thus important clues to the early identification of scleromyositis in seronegative patients.

Interestingly, SSc sine scleroderma is a common presentation in patients with anti-Th/To-positive SSc\textsuperscript{22} and, as shown herein, appears as a common presentation of seronegative scleromyositis. With the benefit of a median follow-up of 6.7 years, five of nine additional patients (total n=16/20, 80%) ultimately met the 2013 ACR/EULAR SSc classification criteria.

Using HEP-2 IIF patterns to subset clinically scleromyositis
When HEP-2 IIF patterns are analysed in seronegative scleromyositis, three clinically relevant subsets emerge: ANA-negative scleromyositis, ANA-positive scleromyositis with a speckled nuclear pattern (AC-4 or AC-5) and ANA-positive scleromyositis with nuclear dots (AC-6 or AC-7).

Although uncommon, HEP-2 IIF-negative scleromyositis was seen in 33% of the patients in this study. All patients had an abnormal nailfold capillaroscopy, ILD

\textbf{SSc sine scleroderma as a clue to early identification of scleromyositis in seronegative patients}

Only 55% of our patients presented SSc skin involvement at myositis diagnosis, and the remaining patients presented with SSc sine scleroderma. Interestingly, most of them (89%) presented, singly or in combination, high titer HEP-2 IIF positivity, new onset Raynaud phenomenon, SSc-type capillaroscopy and/or lower oesophageal dysmotility, which are thus important clues to the early identification of scleromyositis in seronegative patients.

Interestingly, SSc sine scleroderma is a common presentation in patients with anti-Th/To-positive SSc\textsuperscript{22} and, as shown herein, appears as a common presentation of seronegative scleromyositis. With the benefit of a median follow-up of 6.7 years, five of nine additional patients (total n=16/20, 80%) ultimately met the 2013 ACR/EULAR SSc classification criteria.

Using HEP-2 IIF patterns to subset clinically scleromyositis
When HEP-2 IIF patterns are analysed in seronegative scleromyositis, three clinically relevant subsets emerge: ANA-negative scleromyositis, ANA-positive scleromyositis with a speckled nuclear pattern (AC-4 or AC-5) and ANA-positive scleromyositis with nuclear dots (AC-6 or AC-7).

Although uncommon, HEP-2 IIF-negative scleromyositis was seen in 33% of the patients in this study. All patients had an abnormal nailfold capillaroscopy, ILD

\textbf{SSc sine scleroderma as a clue to early identification of scleromyositis in seronegative patients}

Only 55% of our patients presented SSc skin involvement at myositis diagnosis, and the remaining patients presented with SSc sine scleroderma. Interestingly, most of them (89%) presented, singly or in combination, high titer HEP-2 IIF positivity, new onset Raynaud phenomenon, SSc-type capillaroscopy and/or lower oesophageal dysmotility, which are thus important clues to the early identification of scleromyositis in seronegative patients.

Interestingly, SSc sine scleroderma is a common presentation in patients with anti-Th/To-positive SSc\textsuperscript{22} and, as shown herein, appears as a common presentation of seronegative scleromyositis. With the benefit of a median follow-up of 6.7 years, five of nine additional patients (total n=16/20, 80%) ultimately met the 2013 ACR/EULAR SSc classification criteria.

Using HEP-2 IIF patterns to subset clinically scleromyositis
When HEP-2 IIF patterns are analysed in seronegative scleromyositis, three clinically relevant subsets emerge: ANA-negative scleromyositis, ANA-positive scleromyositis with a speckled nuclear pattern (AC-4 or AC-5) and ANA-positive scleromyositis with nuclear dots (AC-6 or AC-7).

Although uncommon, HEP-2 IIF-negative scleromyositis was seen in 33% of the patients in this study. All patients had an abnormal nailfold capillaroscopy, ILD

\textbf{SSc sine scleroderma as a clue to early identification of scleromyositis in seronegative patients}

Only 55% of our patients presented SSc skin involvement at myositis diagnosis, and the remaining patients presented with SSc sine scleroderma. Interestingly, most of them (89%) presented, singly or in combination, high titer HEP-2 IIF positivity, new onset Raynaud phenomenon, SSc-type capillaroscopy and/or lower oesophageal dysmotility, which are thus important clues to the early identification of scleromyositis in seronegative patients.

Interestingly, SSc sine scleroderma is a common presentation in patients with anti-Th/To-positive SSc\textsuperscript{22} and, as shown herein, appears as a common presentation of seronegative scleromyositis. With the benefit of a median follow-up of 6.7 years, five of nine additional patients (total n=16/20, 80%) ultimately met the 2013 ACR/EULAR SSc classification criteria.

Using HEP-2 IIF patterns to subset clinically scleromyositis
When HEP-2 IIF patterns are analysed in seronegative scleromyositis, three clinically relevant subsets emerge: ANA-negative scleromyositis, ANA-positive scleromyositis with a speckled nuclear pattern (AC-4 or AC-5) and ANA-positive scleromyositis with nuclear dots (AC-6 or AC-7).

Although uncommon, HEP-2 IIF-negative scleromyositis was seen in 33% of the patients in this study. All patients had an abnormal nailfold capillaroscopy, ILD
was frequent and, importantly, these patients were at high risk for scleroderma renal crisis, a feared complication of corticosteroid therapy in SSc, yet considered standard therapy in the treatment of myositis. Indeed, in the present study, two of the three HEp-2 IIF-negative patients who developed scleroderma renal crisis did so while treated with corticosteroids for their myositis.

HEp-2 IIF-positive scleromyositis with a speckled pattern (AC-4 or AC-5) was seen in 25% of the patients and was frequently associated with rarer SSc-specific aAbs, including anti-RuvBL1/2, anti-U4/U6RNP and anti-U5RNP. Of note, SSc sine scleroderma was the presenting phenotype in 60% of these patients. Although not as suggestive of SSc as a nucleolar pattern, a speckled...
pattern by IIF is a frequent serological finding in SSC when aAbs other than anti-centromere, anti-topoisomerase I and anti-RNA polymerase III are considered.37

Scleromyositis with nuclear dots on HEp-2 IIF (AC-6 or AC-7) was seen in 30% of our patients, and unearntched anti-SMN aAbs in five of six (83%) patients with this IIF pattern. Anti-SMN aAbs, all associated with nuclear dots on IIF, were originally described in three women with myositis (n=1) and myositis/SSc overlap syndrome (n=2)32 and, in a subsequent report, in a single patient with necrotising myopathy.33 Our data therefore suggest that the nuclear dots pattern may be used as a screening test for identifying anti-SMN aAbs. At last follow-up, all our patients with anti-SMN met the 2013 ACR/EULAR SSc classification criteria. Anti-SMN aAbs may therefore be a novel SSc-specific aAb.

Unique myopathological findings of myositis in SSC

Histopathological studies of muscle biopsies in SSC have demonstrated that myositis should be considered as a distinct feature of SSc.23 24 38 39 The presence of microangiopathy was demonstrated in scleromyositis associated with anti-centromere and anti-topoisomerase I aAbs.40 Necrotising myopathy and nonspecific myositis were the most common histopathological categories observed in SSc with muscle involvement.29 Also, fibrosing myopathy25 and acute neurogenic atrophy29 were recently proposed to be suggestive myopathological SSc findings. The full spectrum of myopathological features of scleromyositis, including in patients with anti-SMN aAbs, remains to be characterised.

Limitations of this study include its retrospective nature and the selection of cases based on expert opinion, given the lack of a gold standard for the definition of scleromyositis. On the other hand, a major strength of this study is the detailed clinical and phenotypic description of previously undescribed seronegative scleromyositis. SSc sine sclerodera was a common presenting SSc phenotype at myositis diagnosis and myositis was commonly the first non-Raynaud manifestation. High titer ANA positivity, new onset Raynaud phenomenon, SSc-type capillarioscopy and/or lower oesophageal dysmotility may be clues to the early identification of seronegative scleromyositis. HEp-2 IIF patterns allowed three novel clinical scleromyositis subsets to emerge. In particular, nuclear dots unearntched scleromyositis associated with anti-SMN aAbs, SSc calcinosis, low incidence of ILD and no scleroderma renal crisis.

Author affiliations

1Division of Rheumatology, Centre hospitalier de l’Université de Montréal (CHUM); Department of Medicine, Université de Montréal, Montreal, QC, Canada
2Centre de Référence des Maladies Autoimmune Rares, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
3Division of Rheumatology, Department of Medicine, Jewish General Hospital; Department of Medicine, McGill University, Montreal, QC, Canada
4Division of Internal Medicine, Department of Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada
5Division of Geriatrics, Department of Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada

REFERENCES


31 Mahler M, Satoh M, Hudson M, et al. Autoantibodies to the Rpp25 component of the Th/To complex are the most common antibodies in patients with systemic sclerosis without antibodies detectable by widely available commercial tests. *J Rheumatol* 2014;41:1334–43.


35 Steen VD, Medsger TA. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum* 1998;41:1613–19.


