Myopathy with antibodies to the signal recognition particle: clinical and pathological features

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Objectives: To study myopathies with serum antibodies to the signal recognition particle (SRP), an unusual, myositis specific antibody associated syndrome that has not been well characterised pathologically.

Methods: Clinical, laboratory, and myopathological features were evaluated in seven consecutive patients with a myopathy and serum anti-SRP antibodies, identified over three years. The anti-SRP myopathy was compared with myopathology in other types of inflammatory and immune myopathies.

Results: The patients with anti-SRP antibodies developed weakness at ages ranging from 32 to 70 years. Onset was seasonal (August to January). Weakness became severe and disability developed rapidly over a period of months. Muscle pain and fatigue were present in some patients. No patient had a dermatomyositis-like rash. Serum creatine kinase was very high (3000 to 25 000 IU/l). Muscle biopsies showed an active myopathy, including muscle fibre necrosis and regeneration. There was prominent endomysial fibrosis, but little or no inflammation. Endomysial capillaries were enlarged, reduced in number, and associated with deposits of the terminal components of complement (C5b-9, membrane attack complex). Strength improved in several patients after corticosteroid treatment.

Conclusions: Myopathies associated with anti-SRP antibodies may produce severe and rapidly progressive weakness and disability. Muscle biopsies show active myopathy with pathological changes in endomysial capillaries but little inflammation. Corticosteroid treatment early in the course of the illness is often followed by improvement in strength. In patients with rapidly progressive myopathies and a high serum creatine kinase but little inflammation on muscle biopsy, measurement of anti-SRP antibodies and pathological examination of muscle, including evaluation of endomysial capillaries, may provide useful information on diagnosis and treatment.

Immune mediated and inflammatory myopathies are usually classified according to their clinical, electrophysiological, serological, and pathological features. Polymyositis is a group of disorders that have in common weakness (usually proximal), a raised serum creatine kinase, a myopathic and irritative pattern of changes on electrodiagnostic testing, and myopathic changes—often associated with inflammation—on pathological examination of muscle. Dermatomyositis has many features that are similar to polymyositis but is distinguished by skin involvement and by muscle pathology that usually includes perifascicular myopathic changes. Inclusion body myositis is distinguished from other inflammatory myopathies by its clinical pattern of patchy, asymmetrical, proximal and distal weakness and pathological changes that include vacuoles and focal invasion of muscle fibres by inflammatory cells. Polymyositis and dermatomyositis are generally thought to be immune mediated, but the pathogenic processes underlying inclusion body myositis are unclear.

It now appears that subgroups of polymyositis and dermatomyositis can be delineated on the basis of clinical, serological, and pathological features of disease syndromes. Some of these myopathy syndromes are associated with characteristic “myositis specific” serum antibodies. The best defined, and most common, of these syndromes is associated with serum antibodies to the Jo-1 antigen (histidyl t-RNA synthetase). Anti-Jo-1 antibodies are associated with a characteristic clinical syndrome that may include muscle weakness and pain, Raynaud’s phenomenon, interstitial lung disease, arthritis, and skin disorders. Pathological features in muscle also distinguish the Jo-1 syndrome from other types of immune myopathy. Characteristic histological features include prominent, but patchy, fragmentation and macrophage inflammation in perimysial connective tissue. Muscle fibre degeneration and regeneration are most marked in perifascicular regions adjoining the connective tissue pathology.

Another myopathy syndrome includes rapidly developing and often severe weakness, and a serum “myositis specific” antibody directed against the signal recognition particle (SRP). The SRP and its membrane associated receptor (SRPR or docking protein), catalyse the targeting of nascent secretory and membrane proteins to the protein translocation apparatus of the endoplasmic reticulum. The role of anti-SRP antibodies in the pathogenesis of the myopathy has not been defined. The anti-SRP associated syndrome has been described clinically in fewer than 20 patients. Pathological features of the myopathy have not been reported in detail. During the past three years we identified seven patients with myopathy syndromes and serum anti-SRP antibodies. We report the features of these patients, who have a characteristic clinical and pathological syndrome.

METHODS
Clinical data
Over a three year period, adult patients presenting to the neuromuscular service at Washington University School of Medicine in St Louis, Missouri, USA with acquired myopathies without other clear causes had serum evaluated for a panel of 12 myositis specific and myositis associated antibodies.

Assays were performed by the Oklahoma Medical Research Foundation (Oklahoma City, Oklahoma, USA) using immunoprecipitation methodology. Assays included studies for antibodies to Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, SRP, PM-Scl, Ku, U1RNP U2RNP and Ro. Results are reported qualitatively as positive or negative.

Our report includes the seven consecutive patients evaluated during this period in whom serum anti-SRP antibodies...
were detected and confirmed by serum immunoprecipitation
and immunodiffusion methods. None of these patients had
positive tests for antibodies to SRP in their serum. Anti-SRP antibodies were not detected in the serum of eight patients with dermatomyositis (five adults and three
children) or in 31 patients with inflammatory myopathies
tested during the same period.

Physicians in our neuromuscular group examined the seven
patients with myopathy and anti-SRP antibodies. All had
muscle biopsies that were evaluated in our neuromuscular
pathology laboratory without knowledge of the antibody sta-
tus of the patient. Clinical data were obtained from clinical
examination and a review of the patients’ case notes. Strength
was evaluated on the MRC scale, and was also measured
quantitatively, in six proximal and three distal muscle groups
bilaterally, using a hand held myometer (Chatillon, Champion
Scane, St Louis, Missouri, USA) and a grip meter (Jaymar,
Preston, New Jersey, USA). 15

We compared the myopathy in our seven patients with
anti-SRP antibodies with muscle changes in 42 patients with
no antibodies to SRP in their serum. Thirty six patients had
definite polymyositis, 16 definite dermatomyositis, 17 or other
subgroups of immune myopathies diagnosed on clinical, sero-
logical, electrophysiological, and pathological grounds. 8 Spe-
cifically, for all these pathology control groups, we included
only biopsies with myopathic, connective tissue, or vascular
involvement. Serum anti-Jo-1 antibodies were confirmed
using immunoprecipitation, as enzyme linked immunono-
sorbent assay (ELISA) methodology alone can give false posi-
tive results. Six control patients had biopsies with no morpho-
logical abnormalities.

Laboratory data
Muscles chosen for biopsy had 4/5 strength (MRC grade). Five
of the seven muscle biopsies were obtained before treatment
with corticosteroids or immunosuppressive agents. The initial
muscle biopsies from patients 2 and 5 were obtained two to
days after the onset of treatment with corticosteroids.
Cryostat sections of rapidly frozen muscle were processed for
muscle histochemistry and immunocytochemistry in a stand-
dard fashion. 15 17 The evaluators (TM and AP) were blinded
to the status of the anti-SRP antibodies at the time of initial
biopsy evaluation and subsequent quantitative analysis.
Immunocytochemistry was performed on biopsies from the
seven patients with anti-SRP antibodies and paired normal
tissue controls for each antibody using standard protocols.
Primary antibodies used in this study were directed against
CD68, CD3, and C5b-9 (membrane attack complex (MAC))
antigens (Sigma, St Louis, Missouri, USA) and human major
histocompatibility complex class I antigen (MHC-1) (US Bio-
logical, Swampscott, Massachusetts, USA). Ulex europaeus
agglutinin I (UEA-1) (Sigma), a lectin that binds to α-fucosyl
residues on endothelial cells, was used as a marker for
capillaries. 18 19 Antibody binding was visualised using peroxi-
dase conjugated secondary antibodies (Sigma).

Data analysis
Light microscopic images from regions randomly chosen for
quantitative analysis were stored digitally. Endomysial vessel
(capillary) density was determined by quantitating the
number of endomysial vessels per 1000 µm2 of muscle fibre
area (capillary index). 20 24 The average endomysial capillary
diameter was calculated from measurements of the smallest
cross sectional diameters of endomysial vessels in randomly
selected regions of digitally stored images of patient and con-
trol muscle biopsies. For analysis of C5b-9 deposition we
examined only endomysial vessels, as antibodies to C5b-9 may
cross the media of perimysial arterioles in normal muscle.
Fishers exact and Mann–Whitney rank sum tests were used
to calculate the statistical significance of differences between
groups.

CASE REPORTS
Patient 1
A 32 year old man was admitted to the hospital with a five
month history of rapidly progressive severe weakness in the
trunk, arms, and legs leading to inability to stand or sit. He
had also noted generalized myalgia, fatigue, dyspnoea, and
weight loss. Neurological examination showed bifacial weak-
ness and severe symmetrical proximal weakness, graded at 0/5
in the lower extremities and 2/5 in the proximal upper
extremities. Sensory and skin examination was normal. Labo-
atory data included raised creatine kinase (CK) at 6204 IU/l
and raised aldolase at 55 IU/l. Electromyography revealed
fibrillations, positive sharp waves, and myopathic motor unit
potentials in proximal and intermediate muscles. Nerve
conduction studies were normal except for a mildly reduced
tibial CMAP amplitude. A muscle biopsy showed an active
myopathy with muscle fibre degeneration and regeneration,
markedly increased connective tissue, and a few small foci of
mononuclear inflammatory cells. High dose intravenous
corticosteroid treatment produced no improvement in
strength.

Patient 2
A 35 year old woman developed weakness in the legs, and then
in the arms, which progressed over 12 months. She also expe-
rienced myalgia, stiffness, and fatigue. Mild dysphagia was
present initially but this did not persist. She was diagnosed as
having polymyositis on clinical grounds, and treated using
oral prednisone with symptomatic improvement in muscle
strength. After two years, steroids were discontinued and the
weakness and fatigue recurred. Reinstitution of prednisone
and the addition of methotrexate and azathioprine were not
effective. Over the next year, weakness progressed. Neurologi-
cal examination showed symmetrical proximal weakness
(3/5). Sensory and skin examination was normal. Laboratory
data included a raised serum CK at 5064 IU/l. Electromyogra-
phy revealed fibrillation potentials, positive sharp waves, and
short duration, early recruited motor unit potentials in proxi-
mal muscles. Nerve conduction studies were normal. A muscle
biopsy showed severe end stage pathology. Treatment with
intravenous methylprednisolone (Solumedrol) (1 g/day for
days) followed by oral prednisone (60 mg/day for several
months) produced mild improvement in functional abilities
and proximal muscle strength.

Patient 3
A 48 year old woman developed weakness in the arms and legs
and generalised fatigue that rapidly progressed over three
months to severe disability with inability to rise from a bed or
chair. She denied significant myalgia, skin changes, or bulbar
or respiratory dysfunction. Neurological examination showed
severe, relatively symmetrical proximal extremity muscle
weakness (0/5 to 1/5) and mild neck flexor weakness (4/5), but
no facial weakness. Serum CK was 24 900 IU/l. Electromyogra-
phy revealed fibrillation potentials, positive sharp waves, and
myopathic motor unit potentials in proximal muscles. A
muscle biopsy showed an active myopathy with degenerating
and regenerating muscle fibres, increased endomysial connec-
tive tissue, and no inflammation. The patient was treated with
oral prednisone (60 mg/day) and azathioprine (50 mg/day) for
two months with no change in symptoms. Drug doses were
increased to 150 mg/day of azathioprine and 80 mg/day of
prednisone. Quantitative muscle strength testing showed pro-
gressive improvement in proximal strength, reaching nearly
normal values by 12 months, and continuing at those values
over the next year with tapering doses of prednisone.

Patient 4
A 46 year old man developed weakness in the arms and legs that
progressed over eight months to severe disability, with need for
Serum CK was 1950 IU/l. A second muscle biopsy showed an active myopathy with many degenerating and regenerating fibres and increased endomysial connective tissue. Treatment with weekly corticosteroids (0.75 to 1 g) for two years was associated with gradual and substantial improvement in strength, including 4/5 values in the proximal arms and legs and 5/5 in more distal muscles.

Table 1 Clinical and laboratory characteristics of the patients

<table>
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<tr>
<th>Clinical features</th>
<th>Patient No</th>
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<td>M</td>
<td>F</td>
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<tr>
<td>Weakness</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>Maximum severity (% of normal strength)</td>
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<td>0%</td>
<td>0%</td>
<td>20%</td>
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<td>+</td>
<td>-</td>
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<td>+</td>
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<td>Steroid response</td>
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<td>Laboratory data</td>
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<td>6204</td>
<td>3064</td>
<td>24 972</td>
<td>8940</td>
<td>7406</td>
<td>25 000</td>
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<td>ND</td>
<td>ND</td>
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<td>23</td>
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<td>-</td>
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<td>sp act</td>
<td>Myopathic;</td>
<td>sp act</td>
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<td>sp act</td>
<td>Myopathic;</td>
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</tr>
</tbody>
</table>
| ND, not determined; −, negative or not present; +, present. EMG, electromyography; ESR, erythrocyte sedimentation rate; F, female; M, male; Myopathic, myopathic EMG with brief, small amplitude, polyphasic motor unit potentials; sp act, spontaneous activity at rest, including fibrillations and positive sharp waves.

A 39 year old woman presented with a two month history of progressive proximal weakness, more in the legs than the arms, and generalised fatigue. A scaly skin rash was noted on her hands, neck, and eyelids. Serum CK was 25 000 IU/l. Treatment with oral prednisone, up to 80 mg/day, was followed by subjectively improved proximal strength. Tapering of the corticosteroid dose was associated with a moderate decline in proximal strength and increased disability. Neurological examination showed severe proximal weakness (0/5 to 3/5) in the arms and legs. Serum CK was mildly elevated at 473 IU/l. Electrodiagnostic testing was consistent with an irritable myopathy. A muscle biopsy revealed myopathic changes with many regenerating and some degenerating muscle fibres, but no inflammation. Increased doses of oral corticosteroids led to a subjective sense of increased strength.

Patient 6

A 70 year old woman presented with a two month history of progressive proximal weakness, exercise induced myalgia, a 2.3 kg (5 pound) weight loss, and mild dyspnoea on exertion. On examination there was severe proximal weakness (1/5 to 2/5). Serum CK was 15 034 IU/l. Electromyography showed fibrillation potentials and positive sharp waves with myopathic motor units in proximal and distal muscles. A muscle biopsy revealed an active myopathy with many degenerating and regenerating fibres but no inflammation. She was treated with corticosteroids, initially oral prednisone (60 mg/day), but when weakness progressed (to 0/5 in some muscles) this was...
changed to pulse dose intravenous, and then oral, methylprednisolone (Solumedrol). Methotrexate (15 mg/week) was also added. Improvement in strength and reduction in dyspnoea began after two months. Quantitative strength testing has shown mild progressive improvement in strength with residual severe weakness in proximal muscles.

RESULTS
Clinical characteristics of patients with anti-SRP antibodies
These data are shown in table 1. Our seven patients with myopathy and anti-SRP antibodies ranged in age from 32 to 70 years, with a mean of 48 years, at the onset of weakness. The onset of weakness in all patients was between August and January, usually in the autumn. Five patients were women. All the patients had a history of proximal weakness that progressed relatively rapidly to severe disability. The time from onset to peak weakness ranged from two to 12 months, with a mean of five months. Six patients had a history of muscle discomfort, such as pain or fatigue, but this was never a primary complaint. Three patients noted dysphagia and two complained of dyspnoea. None had a history of palpitations or malignancy.

On examination all patients had proximal, mostly symmetrical, weakness involving both upper and lower limbs. Weakness was very severe in some proximal muscles in all patients. MRC grades in the weakest muscles ranged from 0/5 in five patients to a maximum of 3/5 (quantitative strength testing reduced to a maximum of 20% of normal) in two patients. The weakest muscles were always the deltoid and psoas. Very distal muscles, such as the intrinsic muscles of the hands and feet, were often only mildly weak or normal. Sensation was normal. One patient had a scaly rash that was not typical of dermatomyositis. After treatment with corticosteroids, six of the seven patients showed improvement on quantitative strength testing. Three patients relapsed, with increased weakness, during steroid tapering. Reintroduction of corticosteroid treatment did not result in the same level of improved strength as was observed initially.

Laboratory data
Laboratory data are shown in table 1. Serum CK was markedly raised at presentation in all seven patients with anti-SRP antibodies, ranging from 3064 to 25 000 IU/l (normal < 170), with a mean of 12 900 IU/l. Aldolase was raised in the four patients tested, ranging from 23 to 174 IU/l (normal < 8). Antinuclear antibodies were found in only one patient. The erythrocyte sedimentation rate (ESR) ranged from 1 to 42 (normal < 30), and was mildly raised in four of the seven patients. Electromyography in all seven patients was consistent with a myopathy, showing small amplitude, brief, polyphasic motor unit potentials. Features of muscle irritability, including spontaneous fibrillation potentials and positive sharp waves, were very prominent.

Muscle pathology in patients with anti-SRP antibodies
These data are shown in tables 2 and 3 and fig 1.

One muscle biopsy (from patient 2) was end stage, with muscle fibres largely replaced by fat. The few remaining muscle fibres were small, rounded, and embedded in abundant connective tissue. Muscle biopsies from the other six patients with anti-SRP antibodies showed myopathic features including prominent variation of muscle fibre size (fig 1). None of

### Table 2: Muscle pathology in patients with anti-SRP antibodies

<table>
<thead>
<tr>
<th>Pathological features</th>
<th>Patient No</th>
</tr>
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<tr>
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<td>1 2 3 4 5 6 7</td>
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<tr>
<td>Time from disease onset to muscle biopsy (months)</td>
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<td>Pathological features</td>
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<tr>
<td>Lymphocytic inflammation</td>
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<tr>
<td>Perimysial</td>
<td>±</td>
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<tr>
<td>Endomysial</td>
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<tr>
<td>Perivascular</td>
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<tr>
<td>Muscle fibre size</td>
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<tr>
<td>Variation</td>
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<tr>
<td>Bimodal</td>
<td>NA</td>
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<tr>
<td>Hypertrophy</td>
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</tr>
<tr>
<td>Hypercontracted fibres</td>
<td>+</td>
</tr>
<tr>
<td>Grouped small round fibres</td>
<td>+</td>
</tr>
<tr>
<td>Perifascicular atrophy</td>
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<tr>
<td>Muscle fibre pathology</td>
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<tr>
<td>Necrosis</td>
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<td>Scattered</td>
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<tr>
<td>Regional (large groups)</td>
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<tr>
<td>Regeneration</td>
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<td>Coarse internal architecture</td>
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<td>Immature (2C) fibres</td>
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<td>Mitochondrial changes</td>
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<tr>
<td>C5b-9 deposition</td>
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<td>Connective tissue features</td>
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<td>Endomysial</td>
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<td>Increased</td>
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<td>Acid phosphatase+/CD68+ cells</td>
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<td>Perimysial</td>
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<td>Fragmentation</td>
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<tr>
<td>Alkaline phosphatase staining</td>
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<td>Acid phosphatase+/CD68+ cells</td>
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<tr>
<td>Vessels</td>
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<td>Capillaries</td>
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<td>Reduced number</td>
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<td>Enlarged size</td>
<td>+</td>
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<tr>
<td>C5b-9 deposition</td>
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NA, tissue type not present for evaluation in biopsy; +, present in biopsy; −, not present in biopsy.
the biopsies showed a perifascicular distribution of atrophic or myopathic changes.

The distribution of muscle fibre sizes often appeared bimodal. One population of muscle fibres was hypertrophied (fig 1, panels A and B). Many dark, rounded, probably hypercontracted, muscle fibres were also observed in two biopsies. The other population of muscle fibres was small, rounded, and often occurred in clusters (fig 1B). Small regenerating muscle fibres (basophilic colour on H&E stain, or intermediate colour on ATPase, pH 4.3) were distributed randomly through most biopsies.

Necrotic muscle fibres (diffuse pale staining and a hyaline appearance with H&E)—often invaded by macrophage-like cells that stained with non-specific esterase, acid phosphatase, and anti-CD68 antibody—were scattered through all six biopsies.

Prominently increased endomysial connective tissue was a feature of five biopsies (fig 1C). In several, the marked increase in connective tissue was especially notable in the light of the short (two to five month) history of weakness. In all biopsies NADH stains showed coarse, irregular internal architecture in many muscle fibres scattered throughout the biopsy.

Mononuclear inflammatory cells were uncommon. No biopsy had perimysial or perivascular accumulations of mononuclear cells. One biopsy showed a single focus of mononuclear cells in the endomysium. Focal cellular invasion of intact muscle fibres was not observed.

Alkaline phosphatase staining of perimysial connective tissue was noted in three patients. Mitochondrial stains reflected the abnormal internal architecture of muscle fibres that was also noted on NADH, but these were otherwise unremarkable.

No biopsies had any muscle fibres with vacuoles. Staining of muscle fibres for MHC-I was absent in three biopsies, present only on scattered regenerating fibres in two, and present in scattered fascicles in small amounts in one.

### Endomysial capillary changes in patients with anti-SRP antibodies

Endomysial capillary density was reduced in muscles from patients with anti-SRP antibodies (fig 2). The mean endomysial capillary index was reduced in muscles from patients with Anti-SRP myopathy. Polymyositis: Jo-1 antibody positive Polymyositis: Jo-1 antibody negative Dermatomyositis Fasciitis Paraneoplastic necrotic myopathy

<table>
<thead>
<tr>
<th>Muscle fibre features</th>
<th>Anti-SRP myopathy</th>
<th>Polymyositis: Jo-1 antibody positive</th>
<th>Polymyositis: Jo-1 antibody negative</th>
<th>Dermatomyositis</th>
<th>Fasciitis</th>
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<td>No of biopsies</td>
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*Based on six rather than seven anti-SRP patients: one muscle biopsy (from patient No 2) had too few muscle fibres for determination of the capillary index.

**Different from other forms of immune myopathy, p < 0.001.

*Different from myositis and fasciitis, p < 0.001.

†Different from dermatomyositis, p < 0.001.

‡Different from polymyositis and fasciitis, p < 0.001.

ND, not determined; +, positive.
anti-SRP antibodies (p = 0.006), measuring 0.7 (0.1) (mean (SD)), compared with values in the normal controls of 1.2 (0.1). Muscle fibre profiles with no neighbouring capillaries were common (fig 2, panel E). Capillary density was uniformly reduced throughout the biopsies.

In normal controls most muscle fibres had several neighbouring capillaries (fig 2, panels A and C). We have previously found—in agreement with other studies—that capillary density is normal in polymyositis and Jo-1 myositis, but reduced in dermatomyositis. The mean diameter of endomysial capillaries was increased in muscle from patients with anti-SRP antibodies (p = 0.001) (fig 2, panels B, D, and E), measuring 9.1 (0.3) µM compared with control values of 6.5 (0.4) µM (fig 2, panels A and C).

Membrane attack complex, the terminal C5b-9 components of complement, was deposited irregularly in endomysial capillaries in all seven biopsies (fig 3). C5b-9 staining was present in capillaries in most endomysial regions of anti-SRP muscles, in contrast to dermatomyositis in which deposition was usually patchy. No biopsy had diffuse staining of C5b-9 within muscle fibres. In one biopsy (patient 1) C5b-9 was deposited around the rim of scattered muscle fibres. Deposition of the terminal C5b-9 components of complement was not found in endomysial vessels in three control muscle biopsies without myopathy, or in the 19 patients with polymyositis.

DISCUSSION

Our study shows that myopathies associated with serum anti-SRP antibodies have characteristic clinical and pathological features. In previous studies anti-SRP antibodies have been associated with a myopathy syndrome which includes onset in the autumn and a rapidly developing severe weakness. Our results emphasise that severe weakness is a prominent clinical feature of the myopathy, occurring in all of our patients. The severity of weakness is often manifest as a complete loss of strength (0/5 on the MRC scale), which develops bilaterally in at least one muscle group. This occurred in five of our seven patients. In contrast, none of our 11 previously reported patients with myopathies associated with anti-Jo-1 antibodies had such severe weakness in any muscles (p = 0.003). Weakness in the anti-SRP antibody patients developed rapidly, with the time from onset to the maximum severity of weakness averaging only five months. The distribution of the weakness, which was symmetrical and predominantly proximal, was similar in all the patients with anti-SRP antibodies. After treatment with corticosteroids, weakness often improved, but only partially. Residual relatively disabling weakness in some muscle groups was the rule. As in other studies of individuals with anti-SRP antibodies, most of our patients complained of muscle discomfort, but the pain was never severe enough to require analgesic treatment. In contrast to previous series, none of our patients complained of palpitations or of other features suggesting cardiac involvement.

The onset of weakness in all our patients fell during the period between August and January. This differs from the onset of the anti-Jo-1 antibody related myopathy syndromes, which generally occurs in the spring. A seasonal pattern of disease onset might suggest an antecedent infectious or other environmental trigger to the anti-SRP antibody syndrome. However, no clear prodromal illness was identified in any of our patients.

A notable laboratory feature in all our patients, which probably reflected the active myopathic process, was the very high serum CK at presentation, ranging from 3064 to 25 000 IU/l, with a mean of 12 944. Serum aldolase was also raised in the four patients who were tested, ranging from 23 to 174 IU/l (normal less than 8). The EMG suggested an active myopathy, showing myopathic motor unit potentials and prominent spontaneous activity in proximal muscles in all the patients. There were few laboratory signs of systemic disease in our patients: the ESR ranged from 1 to 42, with a mean of 27, while antinuclear antibodies were mildly raised in only one patient.

Several different pathological patterns occur in immune and inflammatory myopathies. In some polymyositis

![Figure 2: Endomysial capillary pathology](http://jnnp.bmj.com/)
The capillary pathology in the anti-SRP antibody syndrome with C5b-9 deposition and enlarged lumens and outside diameters is similar to the changes reported in dermatomyositis. However, the capillary pathology, enlarged size, and C5b-9 deposition in the anti-SRP antibody syndrome occurred diffusely throughout the muscle rather than having a patchy distribution as is typical of dermatomyositis. Other differences from dermatomyositis in patients with anti-SRP antibody associated myopathies included the severe diffuse weakness, absence of rash, and, in the muscle biopsy, prominently increased endomysial connective tissue and relatively enlarged muscle fibres that often appeared hypertrophied or hypercontracted. Further, none of our control patients with typical dermatomyositis syndromes had serum anti-SRP antibodies.

Clinical, laboratory, and pathological features of the anti-SRP syndrome also distinguish it from other immune myopathy syndromes (table 4). There are few of the systemic features such as skin disorders, arthritis, interstitial lung disease, or associated neoplasms that occur in other myositis syndromes. The anti-SRP syndrome—with rapidly progressive severe proximal weakness, occasionally associated with prominent weight loss—has clinical similarities to paraneoplastic necrotic myopathies. However, the syndromes differ in their pathology. In paraneoplastic necrotic myopathies, large regions of necrotic C5b-9 positive muscle fibres are typical features,21 while prominently increased endomysial connective tissue or enlarged capillaries are not usually present (table 3). This differs from the muscle pathology in the anti-SRP syndrome, with its appearance of a chronic active myopathy, including prominent endomysial connective tissue and scattered necrotic muscle fibres that are only rarely positive for C5b-9. The explanation for the prominently increased connective tissue in the anti-SRP syndrome might be inhibition of muscle fibre regeneration, or stimulation of fibroblasts by antibodies, as is found in systemic sclerosis24 or fibrogenic cytokines.

Another common feature of anti-SRP myopathies that differs from many immune or inflammatory myopathies is the rarity, or absence, of foci of mononuclear inflammatory cells. Other than the CD68 and acid phosphatase positive cells associated with necrotic muscle fibres, anti-SRP biopsies show few or no foci of perimysial or endomysial mononuclear cells, and no focal invasion of muscle fibres by mononuclear cells. Groups of CD3 positive inflammatory cells were only detected in one patient (patient 1). In contrast to inclusion body myositis and some types of polymyositis,26 MHC-1 antigen was not prominently expressed on muscle fibres, except in scattered regenerating fibres, in most of the biopsies.

The improvement after corticosteroid treatment in patients with myopathies and anti-SRP antibodies suggests that the syndrome may be immune mediated. Several features in muscle biopsies from patients with anti-SRP antibodies support the idea that immune mechanisms, especially humoral factors, may play a role in the pathogenesis of the myopathy. First, perimysial connective tissue showed staining for alkaline phosphatase in biopsies from three anti-SRP patients. In our experience, staining of perimysial connective tissue for alkaline phosphatase occurs commonly in immune mediated myopathies and rarely in muscular dystrophies or inclusion body myositis.7

Second, the most consistent pathological feature suggesting the presence of a humoral immune disorder is the pattern of non-inflammatory capillary pathology in all anti-SRP patients. This pathological pattern is similar to that found in dermatomyositis, a disorder in which humoral immune mechanisms are thought to play a prominent role. The pattern of prominent vascular pathology could suggest that muscle fibre damage in anti-SRP antibody associated myopathies is related to ischaemia. The frequent finding of myopathic grouping—multiple foci of small rounded, muscle fibres that

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Figure 3  Terminal complement complex (C5b-9) in endomysial capillaries. C5b-9 is deposited in a patchy fashion in endothelial regions of scattered, enlarged endomysial capillaries (panel A). A high power image (panel B) shows C5b-9 deposition in four enlarged capillaries surrounding a single muscle fibre. A second high power image (panel C) illustrates the patchy nature of the C5b-9 deposition within the enlarged capillaries. A, bar = 14 µM; B and C, bar = 7 µM. (D) Normal muscle shows no endomysial capillary staining for C5b-9 (bar = 12 µM).
Table 4 Comparative features in selected immune myopathy syndromes

<table>
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<tr>
<th>Myopathy syndrome</th>
<th>Clinical features</th>
<th>Pathological features</th>
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<tbody>
<tr>
<td>SRP antibodies</td>
<td>Onset: autumn, acute, adult</td>
<td>Muscle fibres: degeneration, regeneration. Endomysial</td>
</tr>
<tr>
<td></td>
<td>Weakness: severe, proximal</td>
<td>connective tissue: increased. Endomysial capillaries:</td>
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<td></td>
<td>Serum CK: very high</td>
<td>diffuse pathology, reduced number, enlarged, MAC deposition.</td>
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<td></td>
<td>Steroid responsive</td>
<td>Inflammation: minimal</td>
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<td>Jo-1 antibodies</td>
<td>Onset: spring, adult</td>
<td>Muscle fibres: perifascicular myopathy. Endomysial</td>
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<td>Weakness: moderate, proximal</td>
<td>capillaries: normal. Perimysium: fragmentation. Inflammation:</td>
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<td>Features: interstitial pneumonitis, Raynaud’s, arthritis</td>
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<td>Steroid responsive</td>
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<td>Paraneoplastic (necrotic)</td>
<td>Onset: acute, older adult</td>
<td>Muscle fibres: regional necrosis, MAC deposition in</td>
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<td></td>
<td>Weakness: severe, proximal</td>
<td>sarcoplasm. Inflammation: within muscle fibres; macrophage</td>
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<td>Dermatomyositis</td>
<td>Onset age: child or adult</td>
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<td>Weakness: proximal &gt; distal</td>
<td>connective tissue: normal. Endomysial capillaries:</td>
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<td></td>
<td>Features: rash</td>
<td>regional pathology, reduced number, enlarged, MAC deposition.</td>
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<td>Serum CK: high</td>
<td>Inflammation: perivascular, lymphocytic</td>
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<td>Myositis + mitochondrial abnormalities</td>
<td>Onset age: older adult</td>
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Authors’ affiliations

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Competing interests: none declared

REFERENCES

8 Targoff IN, Johnson AE, Miller FW. Antibody to signal recognition particle in polymyositis. Arthritis Rheum 1990;33:1361–70
Patients with periodic limb movement syndrome (PLMS) experience a series of involuntary leg movements at sleep onset and during sleep. The movements are rhythmic or jerky and range from simple extension of the big toe to movement of the whole leg, with flexion of the knee and hip. They generally occur every 20–40 seconds and last 0.5–5 seconds.

A 65 year old woman was referred to our department for differential diagnosis of suspected sleep apnoea syndrome. At presentation she reported excessive daytime sleepiness and mild snoring. Polysomnography revealed PLMS of both legs, with an index score of 89 (fig 1). When the condition was explained to her, she reflected for a moment and said, “now I know why I can always tell which way around my sheets go on my bed”.

The patient later brought in a fitted terry bedsheet with two well worn areas at one end, corresponding to the position of her feet in bed (fig 2). Ad hoc examination of a new terry sheet showed that repeated rubbing rapidly causes noticeable roughening of the surface. With continuing wear the fabric gradually becomes threadbare and finally tears.

Bedding in disarray is a well known feature of PLMS. The increased use of fitted terry sheets may offer a new diagnostic sign for this syndrome—discrete areas of wear from foot movement in bed.

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