Myopathic Changes Associated With Severe Acute Respiratory Syndrome

A Postmortem Case Series

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Background: The March 2003 outbreak of the severe acute respiratory syndrome (SARS) resulted in significant morbidity and mortality. Muscle weakness and elevated serum creatine kinase levels are commonly encountered in patients with SARS. However, the nature and cause of myopathy associated with a SARS infection are unknown because, to our knowledge, there has been no report of histological or postmortem examination of the skeletal muscle from SARS-infected patients.

Objective: To determine the exact nature of the myopathy associated with SARS.

Method: Postmortem skeletal muscles from 8 consecutive patients who died of SARS in March 2003 were studied under light and electron microscopy as well as immunohistochemistry.

Results: Focal myofiber necrosis was identified in 4 of 8 cases. Macrophage infiltration and regenerative fiber were scanty. All 4 patients treated with a steroid had significant myofiber atrophy. In situ hybridization for coronavirus was negative in all subjects. Viral cultures for coronavirus and examination for viral particles under electron microscopy were performed in 2 patients. The viral culture yielded no organisms and there were no viral particles seen on electron microscopic examination.

Conclusions: There is a spectrum of myopathic changes associated with a SARS infection. Focal myofiber necrosis is common and possibly is immune mediated. Critical illness myopathy and superimposed steroid myopathy may also play an important role in SARS.

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either the quadriceps or the psoas. Tissues from 2 patients were sent for viral cultures for SARS-CoV according to standard protocols. The rest was fixed in formalin. Tissues were processed for in situ hybridization for SARS-CoV in all cases and for electron microscopy (EM) in 2 cases. Paraffin sections were stained for MAC387, IgG, IgM, C3, fibrinogen, CD4, CD8, CD20, and CD68 (all from Dako, Copenhagen, Denmark).

The laboratory and pathologic findings are summarized in the Table. Myofiber necrosis was observed in 4 cases and was the most common feature. The necrotic fibers were mostly single and occasionally were 2 necrotic fibers seen close to one another (Figure 1A). The necrosis was coagulative with condensation and fragmentation of sarcolemmal contents (Figure 1A). In 2 of 4 patients with myofiber necrosis, there was karyorrhexis with nuclear debris scattered over the necrotic cells (Figure 1B, arrow). The debris was visualized as nuclear dusts in some cells. Necrotic fibers were mostly devoid of macrophage infiltrates, although some necrotic fibers attracted some histiocytic infiltrates (Figure 1C and D). In contrast with myofiber necrosis seen in inflammatory myopathy, regenerative fibers were only revealed in 2 cases (Figure 2A). On longitudinal sections, the nuclei were visualized as rows of naked closely packed nuclei (Figure 2B). The necrotic fibers were also seen to accumulate a small amount of IgG, IgM, C3, and fibrinogen (Figure 2C) but without other chronic inflammatory or lymphocytic infiltration. The scanty macrocytic infiltrates could be highlighted in MAC386 or CD68 stain (Figure 2D). In addition, specimens from 4 patients showed severe myofiber atrophy. The atrophic fibers showed extensive pallor in staining and a focal feathery type of dissolution of cytoplasmic contents (Figure 3, arrows). Ultrastructural examination was performed in 2 patients. The focal necrotic fibers were seen with dissolution of myofibrillar architecture and plasma membrane and with the loss of Z disks; but basal lamina was generally preserved (Figure 4). No viral particle was identified at EM. In situ hybridization was negative for SARS-CoV in all of the patients.

![Table. Clinical Features and Pathologic Findings of the 8 Patients With Severe Acute Respiratory Syndrome](#)

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>Duration of Symptom Onset to Death, d</th>
<th>Duration of Mechanical Ventilatory Assistance, d</th>
<th>Concurrent Disease</th>
<th>Highest Serum CK Level Recorded (Reference Range, &lt;218 U/L)</th>
<th>Rocuronium Use, Total Cumulative Dose, and Duration of Treatment</th>
<th>Steroid Use, Total Cumulative Dose, and Duration of Treatment</th>
<th>Myofiber Necrosis†</th>
<th>Macrophage Infiltration‡</th>
<th>Myofiber Atrophy§</th>
<th>Regenerative Fiber§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/44</td>
<td>16</td>
<td>12</td>
<td>Chronic hepatitis B</td>
<td>2046 7.5 g over 12 d Hydrocortisone, 4.4 g over 11 d</td>
<td>++ +</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/M/64</td>
<td>11</td>
<td>4</td>
<td>Diabetes mellitus and alcoholic cirrhosis</td>
<td>421 2.3 g over 4 d Hydrocortisone, 2.0 g over 5 d</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>3/M/79</td>
<td>19</td>
<td>15</td>
<td>Ischemic heart disease</td>
<td>140 8.6 g over 15 d Hydrocortisone, 0.45 g over 3 d</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>4/M/76</td>
<td>10</td>
<td>7</td>
<td>Myelodysplastic syndrome</td>
<td>43 4.2 g over 7 d Hydrocortisone, 2.8 g over 7 d</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>5/M/69</td>
<td>17</td>
<td>1</td>
<td>Chronic rheumatic heart disease</td>
<td>198 None None</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>6/F/81</td>
<td>5</td>
<td>0</td>
<td>Parkinson disease and carcinoma of the lung</td>
<td>331 None None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7/M/49</td>
<td>17</td>
<td>7</td>
<td>Hepatitis B and cirrhosis</td>
<td>Not applicable 4.6 g over 7 d None</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/M/81</td>
<td>10</td>
<td>0</td>
<td>Chronic gastric ulcer and severe aortic regurgitation</td>
<td>16400 None None</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
<td></td>
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</tbody>
</table>

*Myofiber necrosis was categorized as follows: ++ + indicates at least 1 necrotic fiber seen in 10 high-power field (HPF); + +, at least 1 necrotic fiber seen in 20 HPF; and +, at least 1 necrotic fiber seen in 30 HPF.
†Macrophage infiltration was categorized as follows: + indicates rare necrotic fibers show infiltration; ++, a few necrotic fibers show infiltration; and ++++, many necrotic fibers show infiltration.
‡Myofiber atrophy was categorized as follows: + indicates atrophic fibers seen focally; ++, atrophic fibers seen easily with some degenerative changes; and ++++, atrophic fibers seen easily with severe degenerative changes.
§Regenerative fiber was categorized as follows: + indicates regenerative fiber focal and present; −, no regenerative fibers.

![RESULTS](#)

![COMMENT](#)
cal findings: (1) Significant myofiber atrophy was noted in all 4 patients who received intravenous steroid therapy (cumulative dose ranged from 0.45-4.4 g or the equivalent of hydrocortisone). This feature was absent in patients who did not receive steroid therapy. (2) Myofiber necrosis was identified in 4 of 8 cases. It was typically focal with scanty inflammatory infiltrates.

Although myofiber atrophy is characteristic of steroid myopathy, administration of a steroid alone is insufficient to explain the florid atrophy given the relatively short duration of steroid treatment (range, 3-11 days). A plausible explanation would be critical illness myopathy (CIM) that may develop in patients who received mechanical ventilatory assistance and high-dose steroid therapy. Critical illness myopathy is common, and its incidence may range from 33% to 83% in an intensive care unit. Prolonged mechanical ventilatory assistance and use of high-dose steroid therapy were identified as independent predictors for CIM in a prospective study.

In our patients, the use of rocuronium, a steroidal neuromuscular blocking agent, during mechanical ventilation may also contribute to the development of CIM. In previous studies of CIM, both electrodiagnostic tests and histological findings were required for confirmation; however, in view of the uncertain infectious risk during the March 2003 outbreak, electrodiagnostic tests were not performed. Nevertheless, myo-
fiber atrophy and a variable degree of myofiber necrosis, which are typical in CIM, were evident in our series. Although we did not reveal widespread loss of thick (myosin) filaments in the 2 patients processed for EM study, it is still consistent with early CIM as myosin loss may not be apparent until 4 weeks after the administration of intravenous steroid therapy (the longest duration of symptoms before death was 19 days in our group). Therefore, based on clinical generalized flaccid paresis, associated risk factors (use of intravenous steroid therapy, stereoidal muscle relaxant, and mechanical ventilation), elevated serum CK levels, and light microscopy histological features, the diagnosis of probable CIM is tenable. The absence of myofiber atrophy in patients who did not receive steroid therapy suggests that the steroid could be an important cofactor in the pathogenesis of CIM.

As mentioned, the myofiber necrosis observed was focal. It is uncertain whether this predominantly reflected the probable CIM or was also SARS-CoV–related. Other RNA viruses, like influenza virus\textsuperscript{17-19} and hepatitis C virus,\textsuperscript{20} may give rise to similar focal myofiber necrosis. Since SARS-CoV is also an RNA virus, it raised the possibility of SARS-associated myopathy. In addition, in 2 of 4 patients with focal necrosis, no steroid or rocuronium therapy was given. In patient 8, the focal and isolated myofiber necrosis revealed (Figure 1B) may suggest myopathy other than CIM as this patient received neither treatment with a steroid or rocuronium nor mechanical ventilatory assistance. Further investigation for the specificity of this focal myofiber necrosis could be helpful because if such a relationship can be confirmed, similar findings in patients with myopathy or an elevated serum CK level as the predominant feature in the prepneumonic stage should raise the suspicion of SARS.

In the semiquantification of necrotic fibers, there is a suggestion that patients with a higher serum CK level had more extensive myofiber necrosis, and thus, the serum CK level may reflect the severity of myopathy associated with SARS. As 30% of the patients with SARS had elevated serum CK levels, and more than 60% of these patients had myalgia and objective muscle weakness on presentation, myopathy in SARS could actually be common. In our series, all of the patients experienced progressive myalgia and muscle weakness from the early course of the disease. The weakness was typically truncal and symmetrically over the proximal limbs and neck flexors. The facial, ocular, bulbar, and small muscles of the hands were relatively spared. All of our patients had become bed-bound from the myalgia and muscle weakness before the respiratory failure set in. Nevertheless, further assessment was impossible when a neuromuscular blocking agent was used during mechanical ventilation. Further prospective study with a larger sample is needed to confirm the relationship of the serum CK levels and myopathy in SARS.

Because CIM commonly involves respiratory muscles\textsuperscript{12} and is associated with prolonged respiratory failure and difficulties in weaning the patient from mechanical ventilation,\textsuperscript{22} the recognition of probable CIM in this series may influence the future management of SARS. As mechanical ventilation and concomitant high-dose steroid therapy (eg, consecutive pulses of methylprednisolone, 500 mg each) were often used in severe SARS pneumonitis,\textsuperscript{1,23} physicians should carefully weigh the pros and cons of high-dose steroid therapy when one considers that
the resulting CIM may prolong the muscle weakness and respiratory failure and subsequently hinder the rehabilitation of the survivors.10,24

Our study provides preliminary evidence that there is a spectrum of myopathy associated with SARS. This spectrum is common among patients with fatal SARS and may result from CIM and immune response to SARS-CoV. However, there were limitations to the present study. Tissue specimens were not prepared by standard frozen section examination because of the unknown infectious risk at the time of the outbreak, and adenosine triphosphatase staining was not performed. Furthermore, electrophysiological studies that could have been invaluable for screening and assessing the extent of the myopathy were infeasible during the SARS epidemic. Further prospective studies to document the frequency, severity, clinical significance, and interplay of CIM and SARS-associated myopathy are warranted.

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REFERENCES