Myopathic Changes Associated With Severe Acute Respiratory Syndrome

A Postmortem Case Series

Thomas W. Leung, MD; Ka Sing Wong, MD; Andrew C. Hui, MD; Ka Fai To, MD; Sih To Lai, FRCP; Wai Fu Ng, FRCPath; Ho Keung Ng, MD

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.

Arch Neurol. 2005;62:1113-1117

THE SEVERE ACUTE RESPIRATORY syndrome (SARS), which is associated with a novel coronavirus (SARS-CoV), is regarded mainly as a respiratory disease that had led to severe morbidity and mortality in its outbreak in March 2003.1,2 Apart from noticeable lung damage,3 muscle weakness and an elevated serum creatine kinase (CK) level occurred in more than 30% of the SARS-infected patients.1 Elevation of the serum CK level is likely a result of skeletal muscle myopathy because the cardiac isozyme level was typically normal.1 In view of the potential infectious risk to the health care workers, the exact nature of the myopathy is unknown because postmortem examination has been limited to the lungs. Thus, to our knowledge, there has been no report of postmortem study of the myopathy associated with SARS.
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).

### RESULTS

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 1). 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 appearance (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.

### COMMENT

To our knowledge, there has been no previous report about the myopathy associated with SARS. In our postmortem case series, there were 2 characteristic histologi-
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.5-7 Critical illness myopathy is common8,9 and its incidence may range from 33% to 83% in an intensive care unit.7 Prolonged mechanical ventilatory assistance and use of high-dose steroid therapy were identified as independent predictors for CIM in a prospective study.10 In our patients, the use of rocuronium, a steroidal neuromuscular blocking agent, during mechanical ventilation may also contribute to the development of CIM.7 In previous studies of CIM, both electrodiagnostic tests and histological findings were required for confirmation11,12; however, in view of the uncertain infectious risk during the March 2003 outbreak, electrodiagnostic tests were not performed. Nevertheless, myo-

![Figure 1](image1.png)

**Figure 1.** Isolated myofiber necrosis seen in 4 cases of severe acute respiratory syndrome. A, Coagulation and fragmentation of cytoplasmic contents (patient 7 in the psoas). B, Karyorrhectic nuclear debris, in the form of fine nuclear dusts, was observed in some fibers (arrow; patient 8 in the psoas). C, Necrotic fibers may have some macrophage infiltration (patient 5 in the quadriceps). D, Necrotic fibers may be completely devoid of macrophages (patient 1 in the quadriceps). (All hematoxylin-eosin, original magnification ×270.)

![Figure 2](image2.png)

**Figure 2.** Macrophage infiltration; number of regenerative fibers was scanty. A, Focal fiber regeneration was revealed in 1 case (patient 5 in the quadriceps), (hematoxylin-eosin, original magnification ×360). B, Rows of naked atrophic nuclei were seen longitudinally (patient 3 in the psoas), (hematoxylin-eosin, original magnification ×360). C, Accumulation of IgG by infiltrating macrophages (patient 8 in the psoas), (original magnification ×300). D, Macrophage infiltration of necrotic fibers demonstrated by MAC387 (patient 1 in the quadriceps), (original magnification ×300).
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$^{17-19}$ and hepatitis C virus,$^{20}$ 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 in 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 most of the past series of influenza-associated myopathy, viral culture yielded no organisms.$^{17,18,20}$ Although in one previous study the reverse transcription–polymerase chain reaction could demonstrate virions in the muscles of experimental influenza-associated myopathy, they were not thought to be replicative. In our cases, the negative finding of in situ hybridization and viral culture for SARS-CoV, and the absence of viral particles under EM may suggest that the myofiber necrosis could be a result of immune damage from release of various cytokines instead of direct infection of the skeletal muscles.$^{21}$ Damage to the lung in SARS is also considered related to the release of cytokines.$^{3}$

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,$^{7}$ 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$^{12}$ and is associated with prolonged respiratory failure and difficulties in weaning the patient from mechanical ventilation,$^{22}$ 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,$^{1,23}$ 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.\(^\text{10,24}\)

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.

Accepted for Publication: December 7, 2004.

Correspondence: Thomas W. Leung, MD, Department of Medicine and Therapeutics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong (drtleung@cuhk.edu.hk).

Author Contributions: Study concept and design: Leung. Acquisition of data: Leung, Wong, Hui, To, Lai, W. F. Ng, and H. K. Ng. Analysis and interpretation of data: Leung. Drafting of the manuscript: Leung, Wong, and Hui. Critical revision of the manuscript for important intellectual content: Leung, To, Lai, W. F. Ng, and H. K. Ng. Administrative, technical, and material support: Leung, Wong, Hui, To, Lai, and H. K. Ng. Acknowledgement: We thank all of the patients who had SARS and their families for their contributions to our knowledge of SARS.

REFERENCES