Skeletal Muscle and Peripheral Nerve Histopathology in COVID-19

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Neurology® 2021;97:e849-e858. doi:10.1212/WNL.0000000000012344

Abstract

Objective
To explore the spectrum of skeletal muscle and nerve pathology of patients who died after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and to assess for direct viral invasion of these tissues.

Methods
Psoas muscle and femoral nerve sampled from 35 consecutive autopsies of patients who died after SARS-CoV-2 infection and 10 SARS-CoV-2–negative controls were examined under light microscopy. Clinical and laboratory data were obtained by chart review.

Results
In SARS-CoV-2–positive patients, mean age at death was 67.8 years (range 43–96 years), and the duration of symptom onset to death ranged from 1 to 49 days. Four patients had neuromuscular symptoms. Peak creatine kinase was elevated in 74% (mean 959 U/L, range 29–8,413 U/L). Muscle showed type 2 atrophy in 32 patients, necrotizing myopathy in 9, and myositis in 7. Neuritis was seen in 9. Major histocompatibility complex-1 (MHC-1) expression was observed in all cases of necrotizing myopathy and myositis and in 8 additional patients. Abnormal expression of myxovirus resistance protein A (MxA) was present on capillaries in muscle in 9 patients and in nerve in 7 patients. SARS-CoV-2 immunohistochemistry was negative in muscle and nerve in all patients. In the 10 controls, muscle showed type 2 atrophy in 32 patients, necrotizing myopathy in 9, and myositis in 7. Neuritis was seen in 9. Major histocompatibility complex-1 (MHC-1) expression was observed in all cases of necrotizing myopathy and myositis in 8 patients. Abnormal expression of myxovirus resistance protein A (MxA) was present on capillaries in muscle in 9 patients and in nerve in 7 patients. SARS-CoV-2 immunohistochemistry was negative in muscle and nerve in all patients. In the 10 controls, muscle showed type 2 atrophy in all patients, necrotic muscle fibers in 1, MHC-1 expression in nonnecrotic/nonregenerating fibers in 3, MxA expression in capillaries in 2, and inflammatory cells in none, and nerves showed no inflammatory cells or MxA expression.

Conclusions
Muscle and nerve tissue demonstrated inflammatory/immune-mediated damage likely related to release of cytokines. There was no evidence of direct SARS-CoV-2 invasion of these tissues.

Classification of Evidence
This study provides Class IV evidence that muscle and nerve biopsies document a variety of pathologic changes in patients dying of coronavirus disease 2019 (COVID-19).

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with myalgia or fatigue in 11% to 70% of individuals and elevated creatine kinase (CK) elevation in 9% to 33%. Rhabdomyolysis and myositis have been reported, but only a few studies included muscle biopsies, and it is unclear whether muscle damage is the result of viral infection of muscle, toxic effect of cytokines, or another mechanism. In addition, Guillain-Barre syndrome and variants have been described, but studies reporting nerve histopathology are lacking. We report histopathologic findings in skeletal muscle and peripheral nerve from 35 consecutive autopsies performed on patients with coronavirus disease 2019 (COVID-19) who died between April 5, 2020, and June 13, 2020.

Methods

Patient Cohort
All patients with SARS-CoV-2 infection who died between April 5, 2020, and June 13, 2020, and subsequently underwent autopsy at Brigham and Women’s Hospital were included in this study. Informed consent for autopsy was obtained from next of kin or health care proxy of the deceased. Thirty-three patients were diagnosed by positive premortem or perimortem reverse-transcriptase PCR (RT-PCR) of nasopharyngeal swabs, and 2 patients were diagnosed by the presence of SARS-CoV-2 immunoglobulin M or G antibodies (patients 25 and 35). In addition, 10 patients who were negative for SARS-CoV-2 but were critically ill and died during the COVID-19 pandemic were included as negative controls. Patient demographics, clinical data, and laboratory data were extracted from the electronic medical record when available.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Mass General Brigham Human Research Committee on an excess tissue waived consent protocol.

Muscle and Nerve Pathology

Autopsies were performed in a negative-pressure isolation room by personnel equipped with powered air-purifying or N95 respirators. Samples of psoas muscle and femoral nerve were collected for each patient, and tissue was fixed in 10% formalin before standard processing and paraffin embedding. Five-micron-thick sections of psoas muscle were stained with (1) hematoxylin & eosin, (2) Masson trichrome, (3) anti-myosin (skeletal, fast) antibody (Sigma M4276, 1:10,000 dilution, St. Louis, MO), (4) anti-LCA/CD45 antibody (Dako M0701, 1:600 dilution, Glostrup, Denmark), (5) anti–SARS-CoV nucleocapsid antibody (Novus Biologicals NB100-56576, 1:500 dilution, Littleton, CO), and (6) anti-HLA class 1 ABC/major histocompatibility-1 (MHC-1) antibody (Abcam ab70328, 1:15,000 dilution, Cambridge, UK; Leica BOND III immunostainer, antigen retrieval with ER2 and Leica Bond Polymer Refine Detection, Newcastle, UK), and (7) anti-human myxovirus resistance protein A (MxA) antibody (Millipore M143, 1:50 dilution, Burlington, MA; heat-induced epitope retrieval, horseradish peroxidase–conjugated polyclinic goat anti-rabbit immunoglobulin antibody, and DAB chromogen). Femoral nerve sections were stained with (1) hematoxylin & eosin, (2) Masson trichrome, (3) anti-LCA/CD45 antibody, (4) anti–SARS-CoV nucleocapsid antibody, and (5) anti-MxA antibody. Muscle and nerve sections from cases with increased CD45-positive immune infiltrates were also stained with (1) anti-CD4 antibody (Cell Marque EP204, 1:100 dilution, Rocklin, CA), (2) anti-CD8 antibody (Dako CD8/144D, 1:200 dilution), (3) anti-CD20 antibody (Dako L26, 1:250 dilution), and (4) anti-CD68 antibody (Dako PG-M1, 1:200 dilution). Slides were reviewed independently by a board-certified neuropathologist (I.H.S.) and a neurologist board certified in neuromuscular medicine and clinical neuromuscular pathology (A.A.A.).

Statistics

Categorical variables are presented as number (percent). Continuous variables are summarized as mean (range). Statistical comparisons were not performed due to small sample size in each group.

Data Availability

Additional data (tables e-1 and e-2) are available from Dryad (doi.org/10.5061/dryad.wwpzgmsjj). Fully anonymized data will be shared by request from any qualified investigator.

Classification of Evidence

The primary research question of this study was to evaluate the effects of SARS-CoV-2 infection on skeletal muscle and peripheral nerve in patients who died with COVID-19, confirmed by nasopharyngeal swab RT-PCR or serology. This study provides Class IV evidence that muscle and nerve tissue exhibits inflammatory/immune-mediated damage likely related to release of cytokines in the absence of direct SARS-CoV-2 invasion of these tissues.

Results

Clinical Features

Patient demographics, neuromuscular symptoms, and pertinent home and inpatient medications that may affect muscle
Table 1 Demographics and Clinical History in COVID-19 Decedents and COVID-19-Negative Controls

<table>
<thead>
<tr>
<th></th>
<th>COVID-19–Positive Patients (n = 35)</th>
<th>COVID-19–Negative Controls (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at death (range), y</td>
<td>67.8 (43–96)</td>
<td>71.3 (54–84)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>12 (34.2)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td>3 (8.6)</td>
<td>0</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (48.6)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>CKD</td>
<td>7 (20)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Cancer</td>
<td>6 (17.1)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Home medications,a n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>11/26 (42.3)</td>
<td>4/9 (44.4)</td>
</tr>
<tr>
<td>Steroid</td>
<td>2/26 (7.7)</td>
<td>2/9 (22.2)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>1/26 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1/26 (3.8)</td>
<td>1/9 (11.1)</td>
</tr>
<tr>
<td>Immune checkpoint inhibitor</td>
<td>1/26 (3.8)</td>
<td>1/9 (11.1)</td>
</tr>
<tr>
<td>Inpatient medications for COVID-19, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remdesivir</td>
<td>5 (14.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>5 (14.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>4 or 5 (11.4 or 14.3)b NA</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular symptoms, n (%)</td>
<td>4/35 (11.4)</td>
<td>3/10 (30)</td>
</tr>
</tbody>
</table>

Abbreviations: CKD = chronic kidney disease; COVID-19 = coronavirus disease 2019; NA = not applicable.

*a Denominator denotes total number of patients for whom premortem home medications were known.

*b One patient was enrolled in hydroxychloroquine vs placebo trial.

Laboratory Data

Twenty-seven of 35 patients with COVID-19 had CK values available from the hospitalization before death (table e-2, doi.org/10.5061/dryad.wwpzgmsj). Of these, 20 patients (74%) had elevated peak CK with a range of 29 to 8,413 U/L (normal 39–308 U/L for men and 26–192 U/L for women). Nineteen patients had repeat CKs, of which 9 were still elevated before death. Sixteen of the 20 patients also had elevated peak high-sensitivity troponin T levels, of whom 3 had evidence of acute cardiac injury on pathologic examination (patients 1, 24, and 30). Peak white blood cell (WBC) count was elevated in 20 of 27 (74%) patients with a mean of 18.9 × 10^3/μL and range of 1.7 to 64.9 × 10^3/μL (normal 4–10 × 10^3/μL). Peak C-reactive protein was elevated in all 25 patients measured, with a mean of 154 mg/L and range of 6 to >300 mg/L (normal 0–3 mg/L). In the control patients, peak CK was available in only 2 patients (patients C9 and C10) and was elevated at 1,746 and 1,152 U/L, respectively. Peak WBC count was elevated in all 8 patients with available WBC counts, with a mean of 22.1 × 10^3/μL and range of 11.8 to 43.3 × 10^3/μL.

Muscle Histopathology

Microscopic examination of muscle (figure 1 and table 2) showed type 2 fiber atrophy in 32 of 35 patients with COVID-19, a necrotizing myopathy in 9 (no inflammatory cells aside from myophagocytosis of necrotic fibers), and myositis in 7 (defined by perivascular and endomysial inflammatory cell infiltrates). In patients with myositis, CD68-positive, CD4-positive, and/or CD8-positive histiocytes and T cells were observed more frequently than CD20-positive B cells. Diffuse or multifocal MHC-1 immunostaining of nonnecrotic/nonregenerating muscle fibers was evident in all 16 patients with myositis or necrotizing myopathy and in 8 additional patients. One patient (patient 35) exhibited MHC-1 staining predominantly in perifascicular muscle fibers, a finding often seen in dermatomyositis; however, there was no abnormal MxA expression or documentation of clinical features suggestive of dermatomyositis. Abnormal MxA immunostaining was observed in 4 of 9 patients with necrotizing myopathy, 3 of 7 with myositis, and 2 without either. Of these 9 patients, MxA was observed only in the capillaries in 8 and in both myocytes and capillaries in 1 patient. SARS-CoV-2 nucleocapsid immunohistochemistry (IHC) was negative in all 35 cases.

In the 10 control patients, all of whom had multiple medical comorbid conditions, type 2 atrophy was observed in all or peripheral nerve histopathology are presented in table 1 (details for individual patients are provided in table e-1, doi.org/10.5061/dryad.wwpzgmsj). Twelve of 35 patients (34%) were women and 23 (66%) were men. Mean age at death was 67.8 years (range 43–96 years). Time from symptom onset to death ranged from 1 to 49 days, and time from positive SARS-CoV-2 RT–PCR test to death was <1 to 44 days. Four patients complained of myalgia or weakness in arms and legs. Diabetes and connective tissue disease were present in 17 and 3 patients, respectively. Of 26 patients with known premortem home medications, 11 patients were on statins, 2 were on corticosteroids (patients 1 and 6), 1 (patient 25) was on imatinib for gastrointestinal stromal tumor, 1 (patient 27) was on colchicine, and 1 (patient 32) was on pembrolizumab for squamous cell lung cancer. Five patients received tocilizumab; 5 received remdesivir; and 4 or 5 received hydroxychloroquine (1 patient was in a placebo-controlled trial) during hospitalization for COVID-19. One patient received dexamethasone (patient 6) but not specifically for COVID-19. Characteristics of the 10 COVID-19–negative control patients are also shown in table 1 and table e-1. There were no major differences compared to the COVID-19–positive cohort except for a lower prevalence of diabetes in the control group. Three patients in the control group (patients C1, C3, and C5) had neuromuscular complaints of generalized weakness.
patients. One patient (patient C4) had rare necrotic muscle fibers that expressed MHC-1 and MxA; this patient did not have a history of statin use, use of drugs with potential myotoxicity, or cancer. Myositis was not observed in any patients. MHC-1 immunostaining of nonnecrotic/nonregenerating fibers was seen in 3 patients (patients C1, C5, and C8), and MxA immunostaining was seen in 1 patient (patient C8), in addition to patient C4 mentioned above. None of these patients had a documented history of myopathy or connective tissue disease.

Potential associations between histopathologic findings in muscle and medical history were reviewed for COVID-19–positive patients (figure 2). Three of the 9 patients with necrotizing myopathy took statins premortem (patients 4, 10, and 17), which was similar to the proportion of patients without necrotizing myopathy who took statins (8 of 26 patients). However, medication history was not known in 5 of 9 with necrotizing myopathy and in 4 of 26 without necrotizing myopathy. Nevertheless, myotoxicity related to statins and other medications would not be expected to show MHC-1 expression in nonregenerating, nonnecrotic muscle fibers or MxA expression in capillaries. Two of the 7 patients with myositis (patients 1 and 25) and 1 of the 28 patients without myositis (patient 20) had an underlying connective tissue disease. One patient with myositis (patient 32) received 2 cycles of an immune checkpoint inhibitor (pembrolizumab) in the 2 months preceding death. However, none of these patients had a documented history of myopathy associated with these conditions or medication use.

Mean time from onset of COVID-19 symptoms to death was 12.8 days in patients with necrotizing myopathy, 17.1 days in patients with myositis, and 18.1 days in those with neither finding. Statistical comparisons were not performed due to small sample size in each group. Peak WBC count (available in 27 patients) was elevated in 5 of 7 patients (71%) with necrotizing myopathy, 4 of 5 patients (80%) with myositis, and 11 of 15 patients (73%) without either finding. Peak CK was elevated in 10 of 12 patients (83%) with myositis or necrotizing myopathy and laboratory results. Peak CK was also elevated in 10 of 15 patients (67%) without these histopathologic findings, 5 of whom were MHC-1 positive. Associations are best seen in figure 2.

**Nerve Histopathology**

Microscopic examination of nerve showed neuritis in 9 patients (figure 3 and table 2), of whom 4 also had myositis (patients 24, 25, 32, 35). Perivascular inflammatory cells were
observed in 6 patients, endoneurial infiltrates in 1, and both perivascular and endoneurial inflammatory cells in 2. CD68-positive histiocytes were most abundantly observed in all cases but were sometimes copredominant with CD8-positive or, less often, CD4-positive T cells. MxA immunostaining was observed in 7 of 35 (20%) of cases in the capillaries, only 1 of whom had neuritis. SARS-CoV-2 IHC was negative in all 35 cases. Neither inflammatory cell infiltrates nor abnormal MxA expression was observed in the control cases.

Review of medical history for conditions associated with neuritis revealed a history of diabetes in 4 of 9 patients (44%) and 13 of 26 (50%) without neuritis (table 1 and figure 2). History of connective tissue disease was present in 2 patients with neuritis (patients 20, 25) and in 1 without neuritis. One patient with neuritis received pembrolizumab (patient 32); this patient also had myositis, as mentioned above. Of 35 patients, only 2 (patients 6, 23) had a history of polyneuropathy predating SARS-CoV-2 infection. One (patient 6) had a history of diabetes and received chemotherapy (including vincristine) for acute lymphoblastic leukemia but had no inflammation on nerve examination. The other (patient 23) had diabetes and neuritis on histopathology. Mean time from onset of COVID-19 symptoms to death was 13.4 days in patients with neuritis and 17.6 days in patients without neuritis. Peak WBC count was elevated in all 6 patients with neuritis and 14 additional patients (of 27 patients with available laboratory values).

**COVID-19 Therapies**

Twelve patients received tocilizumab, hydroxychloroquine, or remdesivir during hospitalization for COVID-19. While formal statistical analyses were not performed, use of these medications did not appear to be associated with specific histopathologic features in muscle or nerve. Myositis was seen in 1 patient who took tocilizumab (patient 1) and 1 patient who took tocilizumab plus remdesivir (patient 12). Necrotizing myopathy was seen in 1 patient who took hydroxychloroquine (patient 4) and 1 patient who took hydroxychloroquine plus tocilizumab (patient 10). Neuritis was seen in 1 patient who took tocilizumab (patient 26).

**Neuromuscular Symptoms**

Documentation of neuromuscular symptoms or examination during hospitalization for SARS-CoV-2 infection was lacking for most patients. Nonspecific fatigue was not included as a neuromuscular symptom in this study. Four patients had myalgia or subjective weakness affecting arms and legs (patients 4, 10, 14, 16). These 4 patients had type 2 fiber atrophy, necrotic myocytes, and MHC-1 immunostaining on nonnecrotic/nonregenerating muscle fibers. Peak CK levels were elevated at 488 to 2,806 U/L. Nerve histopathology was normal in these 4 patients.

**Discussion**

The pathophysiology of SARS-CoV-2–associated myopathy is poorly understood. The possibility of skeletal muscle infection by the virus has been considered because muscle expresses angiotensin-converting enzyme 2, which is a cell surface receptor used by SARS-CoV-1 and SARS-CoV-2 for host cell entry. Negative SARS-CoV-2 IHC in muscle in our study argues against this hypothesis. However, in 1 study that examined the diaphragm muscle obtained from 26 consecutive autopsies of critically ill COVID-19–infected patients who died, SARS-CoV-2 RNA was found in the muscle in 4 cases (15.4%). In situ hybridization localized the RNA to inside the sarcolemma. This discrepancy with our study findings may be explained by differences in methods to detect the virus or examination of different muscles.

Twenty-four of 35 patients in our study had evidence of an inflammatory or immune-mediated myopathy with necrotic fibers, inflammatory cell infiltrates, or MHC-1 immunostaining of nonnecrotic/nonregenerating muscle fibers. Our observations suggest that muscle damage occurs secondary to an inflammatory response, including damage from cytokines.

To date, literature on skeletal muscle histopathology in COVID-19 is sparse. One study reported muscle biopsy findings in 3 patients infected with SARS-CoV-2 who were

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### Table 2 Muscle and Nerve Histopathology

<table>
<thead>
<tr>
<th></th>
<th>COVID-19–Positive Patients (n = 35)</th>
<th>COVID-19–Negative Controls (n = 10)</th>
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<tbody>
<tr>
<td><strong>Psoas muscle histopathology, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 atrophy</td>
<td>32 (91.4)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Necrotic fibers without inflammation</td>
<td>9 (25.7)</td>
<td>1 (10)</td>
</tr>
<tr>
<td><strong>Inflammation ± necrotic fibers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>7 (20)</td>
<td>0</td>
</tr>
<tr>
<td>MHC-1 IHC</td>
<td>24 (68.6)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>MxA IHC (of capillaries or myocytes)</td>
<td>9 (25.7)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>SARS-CoV-2 IHC</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Femoral nerve histopathology, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>9 (25.7)</td>
<td>0</td>
</tr>
<tr>
<td>MxA IHC (of capillaries)</td>
<td>7 (20)</td>
<td>0</td>
</tr>
<tr>
<td>SARS-CoV-2 IHC</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Abbreviations:** COVID-19 = coronavirus disease 2019; IHC = immunohistochemistry; MHC-1 = major histocompatibility complex 1; MxA = human myxovirus resistance protein A; NA = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* In nonnecrotic, nonregenerating fibers.
clinically suspected of having critical illness myopathy. Biopsies revealed scattered necrotic and regenerating fibers in 1 patient and rare atrophic and regenerative fibers in 2 others. No biopsies stained positive for MHC-1 or membrane attack complex (C5b9). In these patients, the histopathologic findings likely reflected the clinically suspected critical illness myopathy rather than COVID-19–associated myopathy.

Myositis was reported in a 58-year-old patient with SARS-CoV-2 infection with facial weakness, nasal dysarthria, and dysphagia. Muscle biopsy showed perivascular and endomysial inflammation and MHC-1 expression. The patient had a dermatomyositis-specific autoantibody detected in the serum. Viral invasion of muscle was not seen on electron microscopy. Another autopsy series reported myositis in 2 of 10

![Image](https://example.com/image.png)

Heat map showing (A) clinical findings from 35 coronavirus disease 2019 (COVID-19)–positive patients (patients 1–35) and 10 COVID-19–negative control patients (patients C1–C10), including age, sex, relevant medical history (PMH), statin use, and neuromuscular symptoms during hospitalization, and (B) laboratory values for peak creatine kinase (CK) and white blood cell count (WBC). Heat map showing major histopathologic findings in (C) skeletal muscle and (D) peripheral nerve, including presence of necrotic fibers, inflammation assayed by anti-LCA/CD45 immunohistochemistry (IHC), major histocompatibility complex-1 (MHC-1) IHC, human myxovirus resistance protein A (MxA) IHC, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleocapsid protein IHC (right). White boxes indicate data not available. NM = neuromuscular.
autopsies, but it is unclear how myositis was defined. A figure showed necrotic fibers undergoing myophagocytosis in 1 patient. We recently reported a patient with marked weakness and elevated CK (up to 30,000 U/L) who had overexpression of MHC-1 and MxA on perifascicular muscle fibers and capillaries, suggestive of a type-1 interferonopathy. One patient in our autopsy series (patient 35) also had MHC-1 expression on perifascicular muscle fibers but without MxA expression.

How do our findings compare to myopathy associated with other coronavirus infections? In a small post-mortem series of patients who died of SARS-CoV-1 infection, myofiber atrophy and necrosis were also the most common histopathologic findings in skeletal muscle. MHC-1 and MxA staining was not performed. Findings were thought to reflect critical illness myopathy or specific changes of SARS-CoV-1–associated myopathy. Another series found vasculitis in muscle. The virus was not detected in muscle with methods of viral culture, electron microscopy, IHC, or in situ hybridization. One postmortem case report on a patient with cutaneous T-cell lymphoma and Middle East respiratory syndrome coronavirus showed necrotic fibers and an inflammatory infiltrate made up of CD68-positive histiocytes and mixed CD4-positive and CD8-positive T cells. Electron microscopy identified virus-like particles in macrophages infiltrating muscle but not in muscle fibers.

In nerve biopsies, we found perivascular and endoneurial inflammatory cell infiltrates (neuritis) in 9 patients. History of

Figure 3 Femoral Nerve Histopathology

Histologic findings include (A) perivascular and endoneurial inflammation, in the absence of (B) demyelination, comprising mixed (C) CD4, (D) CD8, (E) CD20, and (F) CD68 immune cell infiltrates. (G) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunohistochemistry (IHC) was negative in all cases. (H) Human myxovirus resistance protein A (MxA) IHC highlights scattered capillary cell walls (arrows). Panel H is from patient 19; panels B and G are from patient 20; panel A is from patient 25; and panels C–F are from patient 26. Section from panel A stained with hematoxylin and eosin, panel B with Masson trichrome, panel C with CD4 IHC, panel D with CD8 IHC, panel E with CD20 IHC, panel F with CD68 IHC, panel G with SARS-CoV-2 nucleocapsid IHC, and panel H with MxA IHC. Image in panel A taken with ×20 objective; images in panels B–G with ×40 objective; and images in panel H with ×60 objective.
diabetes was present in 4 patients, connective tissue disease in 2, and immune checkpoint inhibitor use in 1, conditions in which neuritis can be seen.\(^{30,31}\) None had signs or symptoms of Guillain-Barre syndrome. We cannot exclude these conditions as potential etiologies of the observed neuritis (e.g., diabetic lumbosacral radiculoplexus neuropathy or diabetic amyotrophy), although we think these are unlikely to be coincidental occurrences in the patients with inflammatory cell infiltrates in their nerves and MxA expression on capillaries, which would not be seen in these disorders. SARS-CoV-2 was not found in our nerve biopsies by IHC, suggesting that the virus does not infect peripheral nerve.

In contrast to our findings, a CNS-focused postmortem series reported SARS-CoV-2 immunostaining in cranial nerves (glossopharyngeal and vagal nerves), albeit in only 2 of 40 patients, raising the possibility that viral infection of peripheral nerve may occur.\(^{32}\) In that study, SARS-CoV-2 immunostaining was found in undefined cells within the medulla from which these cranial nerves originate. Contiguous spread of infection from the medulla to these cranial nerves is conceivable.

It is possible that viral invasion of muscle and nerve occurred at an earlier stage in the illness and that active viral infection resolved by the time of death, although 22 patients (63%) had detectable SARS-CoV-2 in the lower respiratory tract by IHC, suggesting ongoing infection in other tissues. Viral RNA may be cleared from muscle and nerve tissue due to efficient type 1 interferon response (e.g., including MxA expression) or other mechanisms but not be cleared from more highly burdened organs such as the lungs.

Notably, MxA expression was observed in endothelial cells in 9 of 35 muscle and 7 of 35 nerve biopsies in our autopsy series, which is likely the result of the host response to SARS-CoV-2 infection. MxA is a type 1 interferon-inducible protein that is normally expressed in response to viral infections and prevents viral replication in the host. However, overexpression of type 1 interferons can be toxic, and abnormal expression of MxA in various tissues is seen in type 1 interferonopathies, including dermatomyositis, systemic lupus erythematosus, and idiopathic pernio (chilblains). As mentioned, we previously reported a patient with COVID-19–associated myopathy who had overexpression of MxA on perifascicular muscle fibers and capillaries, as typical of dermatomyositis and suggestive of a type 1 interferonopathy.\(^{15}\) Perniosis with MxA expression in endothelial cells and surrounding dermal and epidermal tissues has been reported in children and young adults late in the course of mild confirmed or presumed COVID-19 infection.\(^{33,34}\) It is speculated that efficient induction of type 1 interferons and activation of the innate immune system quickly eradicate the virus and result in a mild infection but may cause collateral tissue damage. In critically ill patients, similar acral manifestations can occur due to severe thrombotic retiform purpura, in which abnormal MxA expression is not seen.\(^{34}\) Such cases could represent an insufficient type 1 interferon response to the virus. These studies suggest that the type 1 interferon response is protective in viral infection, but overexpression may be toxic to certain tissues. Peripheral nerve and skeletal muscle appear to be bystander victims of the host response and cytokine dysregulation. We suspect that an exaggerated type 1 interferon response might be involved in some cases of COVID-19–associated myopathy and neuropathy. However, the lack of consistent expression in all cases of necrotizing myopathy, myositis, and neuritis and expression in some cases even without these features indicate that other cytokines may be involved in muscle and nerve damage. Abnormal serum levels of several cytokines have been detected in patients with SARS-CoV-2 such as type 1 and gamma interferons, interleukin-1 and -6, and tumor necrosis factor-α, among others.\(^{2,15,35,36}\) We do not think the histopathologic findings in this study simply reflect nonspecific changes in muscle and nerve of patients with severe illness because muscle and nerve biopsies obtained from autopsies of 10 control patients revealed necrotizing myopathy in only 1 patient and no cases with myositis or neuritis.

With regard to laboratory data, we noted that the proportion of SARS-CoV-2–positive patients in our study with elevated CK was higher (74%) than has been reported in other studies (9%–33%).\(^{1,7}\) This is likely explained by the fact that we used peak CK rather than admission CK levels, and our cohort comprised patients with more severe COVID-19. Higher CK levels are associated with poorer outcomes.\(^{37}\) It is possible that cardiac injury contributed to the elevated CK because 16 of the 20 patients with elevated peak CK levels had elevated peak high-sensitivity troponin T levels. However, only 3 of these patients had evidence of acute cardiac injury on pathologic examination. Troponin T may not be specific for cardiac damage and can be elevated in patients with myopathy without cardiac injury,\(^{38}\) concordant with our clinical experience.

There are limitations to this study. First, we did not perform targeted histopathologic examinations of clinically symptomatic muscle and nerve. We do not know whether psoas muscle and femoral nerve were clinically affected. Clinical information was obtained retrospectively, and documentation of neuromuscular symptoms and examinations was limited. These were extremely ill patients who ended up sedated and on ventilators. Three died in the emergency room, and 5 more died within 2 days of admission. The focus on the evaluations of these patients before intubation was stabilization. Second, due to laboratory biosafety concerns, specimens were entirely fixed in formalin for paraffin-embedded sections, and frozen tissue, which is routinely used to assess muscle histopathology, was not available, nor were plastic sections and electron microscopy for muscle and nerve. In addition, because this is a postmortem case series of patients who ultimately died of the virus, our results may not reflect the full spectrum of histopathologic findings in patients with various degrees of illness severity. Our findings may be skewed to those patients with the most severe infections. Last, as mentioned, viral RNA may have been cleared from muscle and nerve tissue before death, possibly due to a robust type 1 interferon response.
Our observations suggest that SARS-CoV-2 is frequently associated with inflammatory cell infiltrates and MxA expression in endothelial cells in both muscle and nerve, as well as necrosis of muscle fibers and abnormal MHC-I expression in muscle. Although we did not measure cytokine levels in blood, the histopathologic abnormalities seen in our patients suggest that these findings may be secondary to the storm of cytokine release rather than direct viral infection of these tissues. Further studies are needed to better understand the pathogenic mechanisms of myopathy and neuropathy associated with SARS-CoV-2.

Acknowledgment

The authors thank the patients and their families. They are grateful for the technical expertise provided by the Brigham and Women’s Hospital autopsy staff (Michelle Siciliano, Jacob Plaisted, John Grzyb) and the staff of the histology, IHC, and neuropathology laboratories (Allyson Campbell, Mark Buchanan, Mei Zheng, Sebastian Valentin, Karen Bryan).

Study Funding

The authors report no targeted funding.

Disclosure

J. Suh, S.S. Mukerji, S.J. Collens, R.F. Padera, Jr, and G.S. Pinkus report no disclosures relevant to the manuscript; A.A. Amato served on medical advisory boards for Alexion, Sarapta, CSL Behring, Strongbridge Pharma, Argenx, Ra Pharmaceuticals, and Orphazyme and is a neurology consultant for Johnson & Johnson (SARS-CoV-2 vaccine study). I.H. Solomon reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by Neurology February 1, 2021. Accepted in final form May 25, 2021.

Appendix

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References


