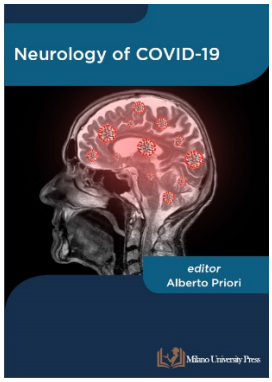

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Chapter 14. **COVID-19-related myopathy**

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List of Contributors

Gianluca Costamagna
Dino Ferrari Centre, Neuroscience Section, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Milan, Italy.
Email: gianluca.costamagna@unimi.it

Daniele Velardo
Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
Email: daniele.velardo@policlinico.mi.it

Giacomo Pietro Comi
Professor of Neurology
Dino Ferrari Centre, Neuroscience Section, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Milan, Italy;
Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
Email: giacomo.comi@unimi.it

Chapter 14. COVID-19-related myopathy

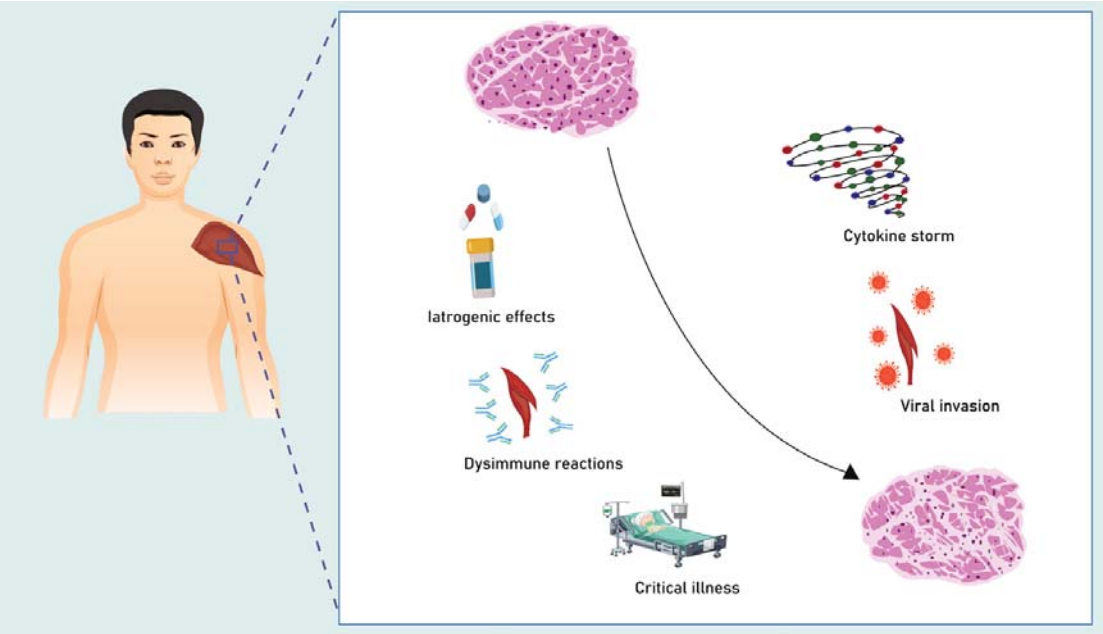
Gianluca Costamagna, Daniele Velardo, Giacomo Pietro Comi

Introduction

Various different viral infections can lead to muscle damage. These include influenza virus A and B, human immunodeficiency virus (HIV), coxsackievirus, cytomegalovirus (CMV), West Nile virus, Dengue virus, Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1), and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)[1-3]

The mechanisms leading to muscle involvement in SARS-CoV-2 infection are still poorly understood. Possible pathogenic mechanisms may involve an acute cytokine release, para- or post-dysimmune dysfunctions, side effects of pharmacologic treatments, critical illness-associated mechanisms, or a direct viral invasion (Figure 14.1).

Figure 14.1: Potential causes associated with SARS-CoV-2 muscle involvement



Different factors may play a role in SARS-CoV-2 myopathies, including iatrogenic effects from systemic drugs and critical illness-related muscular comorbidities. Systemic inflammatory responses known as "cytokine storms", SARS-CoV-2-triggered dysimmune reactions, or direct viral invasion may also lead to muscle damage.

SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) to infect human cells[4]. This receptor is expressed in different organs, including the lungs, the blood vessels, and the immune system[5]. Although there is still no evidence for a direct muscle invasion,skeletal muscles express ACE2 receptors[4], representing a potential viral entry point to the muscle as well. In parallel, SARS-CoV-2 can trigger an inflammatory cascade, increasing interleukin-1, interleukin-6, and tumor necrosis factor release[6] leading to widespread inflammation and possibly muscle damage. Different studies reported small arteriolar and venular thromboses in multiple organs with vasculopathy and vasculitis in severe SARS-CoV-2 infections[7] potentially linked to muscle damage.

Muscular involvement and SARS-CoV-2 infection

Muscular involvement in the context of SARS-CoV-2 infection includes myalgia[8], myositis[9–11] as well as critical-illness myopathies[14].

Myalgia

The literature on muscular involvement in the context of SARS-CoV-2 infection is highly heterogeneous, including mainly case reports and retrospective analyses (Table 14.1).

Most studies report myalgia as the most frequent muscular symptom. Muscle involvement was first described in a retrospective study of 214 Chinese patients[8] where 23 (10.7%) were reported with "skeletal muscle injury." No specific investigations were carried out to further characterize the type and pathophysiology of the muscle injury. In another study involving 41 infected Chinese patients, 18 (44%) complained about myalgia and fatigue. In particular, all 18 patients complained about myalgia as symptom onset; of these, 7 patients required admission to an intensive care unit (ICU)[8] for SARS-CoV-2 infection. In a retrospective study in a European cohort of 1,420 patients, Lechien et al. reported 887 (62.5%) patients with myalgia[15]. In a population of 48 patients with neuromuscular disorders with SARS-CoV-2 infection from different Italian centers, 14 (29.2%) reported myalgia (G Costamagna, unpublished data, 2021).

Table 14.1 Selected case reports/series and observational studies on SARS-CoV-2-associated myopathies

N. of patients	Age	Sex	Signs and symptoms	CK levels	EMG	Muscle biopsy	Ref.
887	NR	NR	Myalgia	NR	NR	NR	15
164	NR	NR	Myalgia, fatigue	≥200 U/L in 90	NR	NR	16
67	NR	NR	Myalgia	NR	NR	NR	17
48	NR	NR	Myalgia	NR	Normal	NR	18
23	NR	NR	Myalgia	>200 U/L in 23	NR	NR	19
18	NR	NR	Myalgia, fatigue	NR	NR	NR	8
11	NR	NR	Myalgia	NR	NR	NR	20
6	NR	NR	NR	NR	NR	Myositis	21
5	NR	NR	Myalgia	> 200 U/l in 6	NR	NR	22
5	NR	NR	NR	> 200 U/l in 5	NR	NR	23
4	8-15	2M, 2 F	Weakness	NR	Myogenic	NR	24
1	60	M	Weakness	11,842	NR	NR	12
1	58	F	Weakness	700	Fibrillations	Myositis	25
1	71	M	Weakness, Myalgia	8720	NR	NR	26
1	16	M	Weakness, fatigue	427,656	NR	NR	27
1	38	M	Myalgia	42,670	NR	NR	28
1	NR	M	Weakness, Myalgia	25,384	NR	NR	9
1	57	F	Weakness	15,000	Myogenic	Necrotizing myopathy	29
1	38	M	Weakness	29,000	NR	Type I Interferonopathy	11

CK: creatine kinase; EMG: electromyography; Ref.: reference; NR: not reported.

Available studies on myalgia and creatinine kinase (CK) levels in SARS-CoV-2 patients in different populations reported mixed results. In a cohort of 138 infected Chinese patients, including 48 subjects presenting with myalgia, CK levels were normal in most cases[18]. In a Chinese study on 1,099 patients, 164 (14.9%) reported myalgia. In another cohort, only 60 patients out of 657 (13.7%) presented increased CK to > 200 U/L[16]. In a sample of 1,150 SARS-CoV-2 patients in the US, 67 (26%) presented with myalgia. Increased CK was reported in some patients, although the exact number was not reported[17]. In a study of 351 European SARS-CoV-2 patients, 95 (27%) showed increased CK levels that were significantly correlated with inflammation markers and disease severity[30].

Altogether, these studies suggest the presence of myalgia and variable degrees of CK elevation to be associated with SARS-CoV-2 infection. However, the heterogeneous populations, the variable assessment of muscle involvement, and the absence of data from patient medical records on pre-infectious muscular diseases limit the generalizability of these findings. In addition, none of these studies prospectively investigated post-infectious muscle damage.

Myositis and rhabdomyolysis

Single case reports and small case series have described muscular damage in the context of SARS-CoV-2 infection presenting as myositis and rhabdomyolysis. Manzano et al. presented the case of a SARS-CoV-2 infected 38-year-old man with an acute-onset, generalized muscle weakness more severe proximally than distally, who was unable to walk. Laboratory testing showed markedly increased CK levels (29,000 U/L). Muscle biopsy revealed some features typically associated with type I interferonopathies, a group of autoinflammatory disorders with prominent enhanced type I interferon signaling[31]. Histopathological alterations included abnormal expression of major-histocompatibility-complex class I and abnormal myxovirus resistance protein A, suggesting a role for SARS-CoV-2 in causing type I interferonopathy-associated muscle damage[11]. Treatment with intravenous remdesevir and methylprednisolone followed by oral prednisone led to mild clinical improvement and improvement in CK levels.

A 16-year-old female patient presented with acute rhabdomyolysis and magnetic resonance imaging (MRI), electromyography (EMG), and bioptic signs of myositis in the context of SARS-CoV-2 infection (G Costamagna, unpublished observations, 2021). She was brought to the emergency department following a transitory loss of consciousness, new-onset mild fever, and severe muscle pain. She had complained about persistent, mild muscle pain in the proximal lower and upper limbs two months previously; no specific tests had been carried out. Upon arrival at our center, laboratory findings showed severe CK elevation (10,988 U/L), increased alanine aminotransferase (ALT), aspartate aminotransaminase (AST), troponin T and lactate dehydrogenase (LDH) levels. EKG and transthoracic echocardiogram ruled out acute myocardial infarction. Renal function was within normal limits. A nasal swab tested positive for SARS-CoV-2. A diagnosis of acute rhabdomyolysis associated with SARS-CoV-2 was made. Early aggressive fluid resuscitation with isotonic saline was initiated. A dermatological evaluation highlighted diffuse skin thickening and hardening on the neck, chest, and thighs consistent with cutaneous manifestations of systemic sclerosis (SS). Extensive autoimmune panel and comprehensive viral and bacterial serology showed ANA positivity (1:640) and SARS-CoV-2 IgM and IgG antibodies. Muscle MRI revealed diffuse muscle and fascial edema with mild and patchy contrast enhancement in the lower limbs. EMG documented diffuse fibrillation potentials with myogenic pattern in the lower limbs. Figure

14.2 shows muscle biopsy findings consistent with inflammatory myopathy (see histopathological studies). A diagnosis of acute rhabdomyolysis associated with SARS-CoV-2 infection in the context of an SS-related inflammatory myopathy was made. A 5-day course with intravenous methylprednisolone followed by high-dose oral dexamethasone led to clinical improvement.

Other reports described MRI-confirmed myositis associated with SARS-CoV-2 infection. A previously healthy patient complained about acute-onset, diffuse myalgias, and proximal lower limb muscle weakness associated with falls. Clinical examination and early laboratory findings including CK levels were consistent with an acute myopathy. Work-up for polymyositis, dermatomyositis and necrotizing autoimmune myopathies (NAM) with comprehensive autoimmunity screening were all negative. On day 7, lower limb MRI showed obturator muscle and quadricipital edema, suggesting a bilateral lower-limb myositis[9].

In another study, a 58-year-old female presented with limb and facial weakness, ptosis, CK elevation, diffuse muscle edema on muscle MRI and myogenic alteration on EMG, with a final diagnosis of myositis following muscle biopsy[25]. The authors reported an improvement in symptoms after a 5-day course of intravenous methylprednisolone and tocilizumab. Shabbir et al. highlighted the case of a middle-aged woman with a history of chronic myopericarditis presenting with SARS-CoV-2 pulmonary symptoms and central chest pain. She developed bilateral leg weakness and elevated CK levels up to 19,000 U/L six days after symptom onset. Lower limb MRI revealed generalized subcutaneous edema and symmetrical diffuse alterations in all muscle compartments, pointing to myositis. Cardiac MRI showed myocardial edema and pericardial effusion, consistent with myopericarditis. Following treatment with colchicine, ibuprofen, and prednisolone, the patient showed both cardiac and muscular improvement upon discharge. Similar to these findings, an MRI study on 7 SARS-CoV-2 infected patients showed intramuscular edema and/or enhancement, supporting the evidence of a possible lumbar spine myositis in some patients[10]. In a case series of 10 SARS-CoV-2 patients from Brazil, minimally invasive, ultrasound-guided, post-mortem morphological studies highlighted features of myositis in 60% of cases and necrotic muscle fibers in 80% of patients[21].

Although a thorough muscular diagnostic work-up was not performed, different authors have described SARS-CoV-2 patients with markedly increased levels of CK, suggesting acute rhabdomyolysis. For example, Zhang et al. highlighted the case of a 38-year-old man with SARS-CoV-2 pulmonary symptoms, muscle weakness, markedly elevated inflammatory markers, elevated ALT, LDH, and CK elevation up to 43,000 U/L[28]. Similarly, other manuscripts report patients with increased levels of CK at disease onset[32] or during hospital stay[12].

However, since these early reports lack a full muscle diagnostic workup (e.g., muscle MRI, EMG, muscle biopsy), confounding factors such as iatrogenic or critical illness-associated effects cannot be ruled out.

Necrotizing autoimmune myopathies

One case report described a possible association between necrotizing autoimmune myopathies (NAM) and SARS-CoV-2 infection. NAM refers to a subgroup of inflammatory myopathies displaying necrotic muscle fibers and absent or minimal inflammation on muscle biopsy. While NAM cases are usually idiopathic, patients taking statins or presenting viral infections or neoplastic diseases may develop this condition[33]. Though the exact pathophysiology of NAM is unknown, some studies suggest a role for an exaggerated inflammatory response, possibly as a result of viral infections[34].

Veyseh et al. described the case of a 57-year-old woman presenting with acute rhabdomyolysis, diffuse muscle weakness, and positive SARS-CoV-2 IgG titers one month from SARS-CoV-2-related, self-limiting, mild upper respiratory symptoms[29]. The patient was discharged with a final diagnosis of rhabdomyolysis in the setting of SARS-CoV-2 infection. Four months later, she presented to the hospital with progressive muscle weakness over 2 weeks. Lower limb MRI showed bilateral, diffuse signal abnormalities in the proximal muscles with edema of the myofascial layers, consistent with myositis. EMG displayed an irritative myogenic pattern in the tibialis anterior muscles. Muscle biopsy showed a few scattered necrotic myofibers with limited inflammatory cell infiltrates, suggesting NAM. Potential confounding factors including acute viral infections, electrolyte abnormalities, endocrinopathies, and statin use were ruled out. Serologic testing was positive for ANA (1:320, speckled pattern) and low titers of anti-Smith antibodies (considered secondary to SARS-CoV-2 infection) with negative titers for anti-Jo1, anti-HMG-CoA reductase (HMGCoAR), and anti-signal recognition particle (SRP). High-dose prednisone (1 mg/kg) led to an improvement in muscle strength and decreasing CK levels. The authors interpreted these findings as a SARS-CoV-2 IgG-related NAM.

Although this report suggests a possible post-SARS-CoV-2 autoimmune response targeting the muscles, there have been no reliable reports of viral-triggered autoimmune muscular disorders.

Critical illness myopathy

Available reports have described ICU-acquired weakness (ICUAW) in severe SARS-CoV-2 cases. ICUAW is typically generalized, symmetrical, affecting both limbs more proximally than distally, as well as respiratory muscles while sparing facial and ocular muscles[35,36]. Diaphragm dysfunction may develop more frequently than limb weakness[37]. Reduction in muscle tone and normal to reduced deep tendon reflexes complete the clinical presentation. Both neurogenic disorders known as critical illness polyneuropathy (CIP) and myogenic abnormalities referred to as critical illness myopathy (CIM) can cause ICUAW[36]. Bolton's and Lacomi's criteria support the diagnosis of these conditions[38,39].

Table 14.2 shows the typical features of CIP and CIM in electrophysiological and biopsy studies.

Table 14.2 Features of critical illness polyneuropathy and critical illness myopathy in electrophysiological and biopsy studies

	Critical illness myopathy	Critical illness neuropathy
CMAP amplitude	Decreased	Decreased
CMAP duration	Increased	Normal
SNAP amplitude	Normal	Decreased
Nerve conduction velocity	Normal or near normal	Normal or near normal
EMG at rest	Fibrillation potentials/positive sharp waves	Fibrillation potentials/positive sharp waves
MUP voluntary muscle activation	Short duration/low amplitude	Long duration, high amplitude, polyphasic
Repetitive nerve stimulation	Absence of decremental response	Absence of decremental response
Direct muscle stimulation	Reduced muscle excitability	Normal muscle excitability
Muscle biopsy	Different abnormalities: myofiber atrophy, angulated fibers, necrosis, fatty degeneration, local or diffuse lack of thick filaments.	Denervation atrophy of type 1 and 2 muscle fibers
Nerve biopsy	Normal	Primary distal axonal degeneration of sensory nerve fibers, no demyelination

CMAP: compound muscle action potential; SNAP: sensory nerve action potential; EMG: electromyography; MUP: muscle action potential.[36,40-42].

Several risk factors can contribute to CIM onset. Among these, the severity of the underlying illness, sepsis and inflammation, multiple organ failure, and mechanical ventilation play an important role[40,43-45]. In addition to these, hyperglycemia, parenteral nutrition, drugs such as corticosteroids, neuromuscular blocking agents, antibiotics (e.g., aminoglycosides and vancomycin), sedatives[46], as well as prolonged immobilization all represent important risk factors[47-49]

Assessment of weakness in patients with CIM includes mainly clinical and electrophysiological evaluations. The most widely used clinical approach is the 6-grade Medical Research Council (MRC) sum score[35]. Other less frequently used tools are the hand-held dynamometry, the Scored Physical Function in Intensive Care Test, the Functional Status Score for the ICU, and the Chelsea Critical Care Physical Assessment Tool[50,51]. The 6-minute walking distance test is useful for patients' performance at discharge or in post-ICU settings[51].

Electrophysiological studies may be valuable tools in unconscious / non-cooperative patients, such as severe SARS-CoV-2 cases. EMG, single-nerve conduction studies (NCS), and direct muscle stimulation (DMS) can help to differentiate CIM from CIP and other differential diagnoses[41,52].

Different case reports[14,53] and small retrospective studies present severe SARS-CoV-2 patients with ICUAW, including CIM. Van Aerde et al. reported a 70% incidence of weakness on awakening in a cohort of 50 SARS-CoV-2 patients requiring invasive mechanical ventilation[54]. Among 11 patients with severe SARS-CoV-2 and ICUAW, 7 received a diagnosis of CIM[55]. In particular, these patients presented mixed muscular electrophysiological alterations on EMG such as abundant spontaneous activity and short motor unit potentials with decreased amplitude and duration. Weak patients presented prolonged ventilation, higher mean morning glycemia, and higher exposure to corticosteroids, sedatives, and analgesics[54]. Madia et al. described 6 ventilator-dependent SARS-induced ARDS cases with acute-onset flaccid quadriplegia noted when attempts were made to reduce sedation[56]. Physical examination showed quadriplegia, weak tendon reflexes, no sensory abnormalities, and preserved extraocular, mimic, and tongue muscles. Electrophysiological studies including EMG and electroneurography (ENG) revealed myopathic abnormalities with fibrillation potentials and rapid recruitment of small, polyphasic motor units in proximal and distal limb muscles, as well as reduced compound muscle action potential (CMAP) amplitude. CK levels were normal or mildly elevated in all patients. One of the patients died due to sepsis, while the others showed improvement in the neurological examination at discharge after 14-20 days.

Taken together, these findings suggest the frequent association between muscle involvement and SARS-CoV-2 infection, particularly in severe cases in ICU settings.

Testing

Specific testing including imaging, electrodiagnostic and histopathological studies can help characterize SARS-CoV-2-associated myopathies.

Neuroimaging studies

MRI can support the diagnosis and evaluation of muscular manifestations and iatrogenic complications associated with SARS-CoV-2 infection[57]. Myositis can present with rhabdomyolysis following damage of the muscle (myonecrosis) and elevated levels of myoglobin in the blood (myoglobinemia). Rhabdomyolysis can be life-threatening, potentially leading to acute kidney failure, compartment syndrome, and disseminated intravascular coagulation[58].

In this context, MRI imaging is the modality of choice for supporting the diagnosis and delineating the site for muscle biopsy, preferably with 1.5-T or 3.0-T magnets, including multiplanar fluid-sensitive and anatomic sequences.

Myositis can be associated with different alterations on muscle MRI, such as muscle edema. Increased signal intensity on T2-weighted or short tau inversion recovery (STIR) sequences identifies muscle edema[59]. Two different radiological patterns define myositis, including homogeneous hyperintense signal and enhancement (type 1) and heterogeneous hyperintense signal and rim enhancement (type 2)[60]. Severe disease forms may display areas of necrosis and loss of muscle architecture. In particular, the "stipple sign" refers to a distinguishing sign of myonecrosis, presenting with dot-like, streaky, or curvilinear enhancing foci within a muscle separated from normal tissue by an enhancing rim61. Intramuscular hemorrhage may be present, identified by T1 hyperintensities or blooming artifacts on gradient-echo sequences[62].

In addition to myositis, CIM represents the most important differential diagnosis for muscle edema on muscle MRI in hospitalized SARS-CoV-2 patients. CIM is associated with non-specific imaging findings such as multifocal muscle edema and atrophy59. In contrast to SARS-CoV-2-related rhabdomyolysis, there is no evidence of necrosis on MRI. Clinical and imaging features of CIM in SARS-CoV-2-infected patients do not appear to differ from CIM in non-SARS-CoV-2 patients.

Imaging is also helpful to monitor diaphragm function. Patients with severe SARS-CoV-2 infection can present diaphragm dysfunction due to CIM, use of ventilators, or phrenic nerve injury, possibly from chest support devices. In addition, diaphragm impairment may be due to a direct SARS-CoV-2 involvement[63]. In an autopsy study on the human diaphragm of ICU SARS-CoV-2 patients, Shi et al. demonstrated the expression of ACE2, the presence of SARS-CoV-2 RNA, and the increased activity of genes related to fibrinogenesis. The fluoroscopy sniff test enables the evaluation of diaphragm excursion and ultrasound offers additional information on muscle atrophy, muscle thickening ratio, and excursion[59,64]. High-resolution ultrasound contributes to the assessment of the phrenic nerve in the neck region, helping in the differential diagnosis between neuropathic versus myopathic processes.

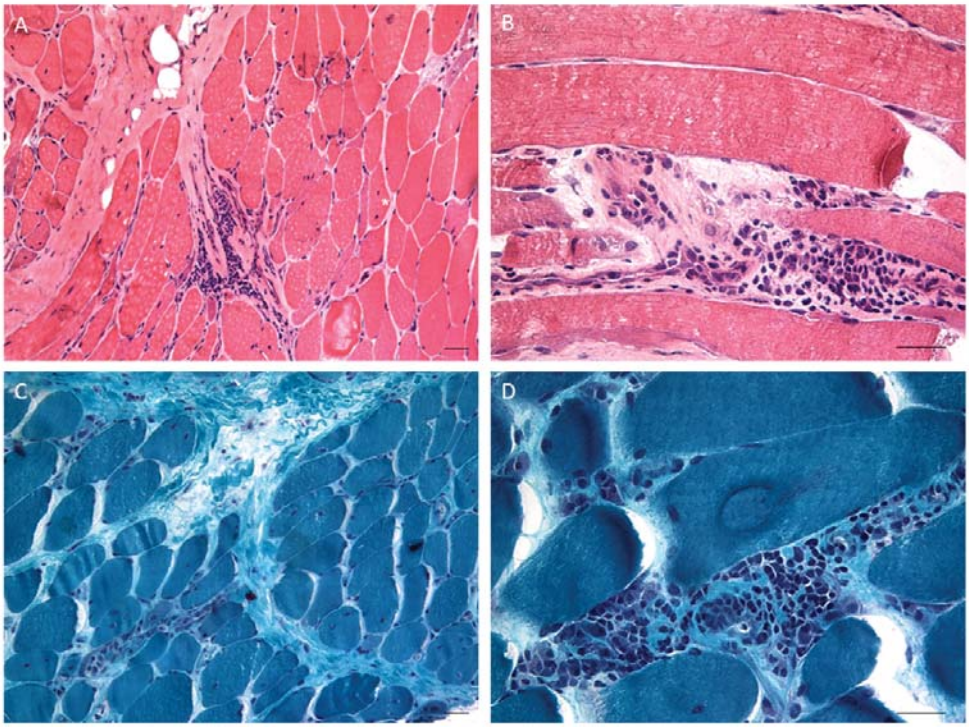
MRI imaging allows the evaluation of other SARS-CoV-2-associated muscular changes, such as sarcopenia and cachexia in patients with prolonged weakness. Sarcopenia is defined as muscle loss typically associated with aging, though other contributing factors include inactivity and poor nutrition. Cachexia is associated with muscle wasting due to chronic illness. Typical MRI findings, in this case, encompass muscle atrophy associated with decreased muscle size and fat infiltration[59].

Electrodiagnostic studies

Few studies have focused on the electrodiagnostic assessment of SARS-CoV-2 patients with muscle weakness. Most case reports / series included patients with severe SARS-CoV-2 infections, possibly presenting with CIM. Cabañes-Martínez performed electrodiagnostic assessment in a cohort of 12 ICU SARS-CoV-2

patients with ICUAW. Seven out of 12 patients showed some degrees of EMG abnormalities, including abundant spontaneous activity, motor unit potential with decreased amplitude and duration. Repetitive nerve stimulation was normal in all cases[55]. Similarly, in another study, 8 SARS-CoV-2 subjects out of 23 patients showed increased spontaneous activity on EMG[65]. A 62-year-old woman with severe SARS-CoV-2 presented motor unit action potentials (MUAPs) with short duration and low amplitude as well as early recruitment, more evident in the quadriceps. On DMS, the post-DMS CMAP was absent in the quadriceps and of reduced amplitude in the tibialis anterior. The ratio of the amplitudes of the CMAP achieved by motor nerve stimulation and DMS is useful to differentiate between neuropathic and myopathic processes, with values near 1 suggesting a myopathic disorder[66]. In this case, the ratio of the CMAP amplitudes achieved by peroneal nerve stimulation and DMS of the tibialis anterior was 0.96, supporting the diagnosis of SARS-CoV-2-related myopathy[14]. A case series of 3 patients with post-SARS-CoV-2 infection myalgia and fatigue showed EMG alterations consistent with myopathies, including MUAP with early recruitment, short duration, and low amplitude in proximal muscles[67].

Figure 14.2: Muscle biopsy of a 16-year-old female patient with a suspected systemic sclerosis-related inflammatory myopathy and SARS-CoV-2 infection



A (20x) and **B** (40x) show scattered necrotic fibers with macrophage infiltration. *Increased centralized nuclei and fiber splitting are also present (hematoxylin & eosin stain, light microscopy). **C** (20x) and **D** (40x) display perivascular inflammatory cell infiltrates and slightly increased endomysial fibrosis (Gomori's trichrome stain, light microscopy).

Overall, these studies suggest no specific electrodiagnostic patterns associated with SARS-CoV-2 myopathies. However, patients with severe SARS-CoV-2 infections may present a more abundant spontaneous activity if compared with patients in the ICU for other etiologies[55].

Histopathological studies

Muscle biopsy may be useful in the differential diagnosis of SARS-CoV-2-associated myopathies (Figure 14.2).

Manzano et al. performed a muscle biopsy of the left deltoid in a patient with a suspected SARS-CoV-2 inflammatory myopathy, showing mild perivascular inflammation in a few vessels without regenerating fibers or perifascicular atrophy. Immunohistochemical analysis displayed abnormal expression of the major histocompatibility complex class I antigen on sarcolemma and sarcoplasm. In addition, abnormal expression of the myxovirus resistance protein A on muscle fibers and capillaries was seen with no membrane attack complex deposition on muscle fibers or vessels. No SARS-CoV-2 RNA was present in the sample[11]. Myxovirus resistance protein A (a type I interferon-inducible protein) can accumulate in muscle fibers and capillaries as an early sign of dermatomyositis preceding muscular atrophy. However, its abnormal deposition may present also following viral infections, including SARS-CoV-2[68]. In addition, muscle tissue lacked deposition of membrane attack complex on capillaries, another sign of dermatomyositis. The authors made a final diagnosis of SARS-CoV-2-associated myopathy caused by type I interferonopathy.

Severe cases of SARS-CoV-2 infection may show consistent vascular pathology on histopathological assessment. In a post-mortem evaluation of a middle-aged woman with rapidly progressive and systemic SARS-CoV-2 infection, Hooper et al. detected diffuse fibrin microthrombi, perimysial microhemorrhages, muscle fiber vacuolar degeneration, and necrosis on muscle tissue[69]. Further analysis revealed no angulated atrophic fibers, basophilic regenerating fibers or increased central nuclei, and only minimal inflammatory infiltrates. Electron microscopy showed no clear signs of direct viral-induced muscle damage. In this case, muscle involvement was more likely due to endothelial injury and vascular damage rather than direct viral infection.

Similarly, in another report on a patient with a suspected SARS-CoV-2-associated myopathy presenting with acute proximal and bulbar weakness, muscle biopsy highlighted features consistent with an inflammatory etiology[25]. These included perivascular inflammatory infiltration with endomysial extension, regenerating fibers (as suggested by mild sarcoplasmic basophilia and enlargement of visible nuclei), and upregulation of human leukocyte antigen class ABC expression on non-necrotic fibers. Cytochrome oxidase / succinic dehydrogenase enzyme histochemistry was unrevealing.

In a case series including 3 muscle biopsies in severe SARS-CoV-2 cases, the findings suggested a non-specific degenerative-regenerative process, supporting a diagnosis of CIM[55]. In particular, 2 patients presented only occasional atrophic and regenerative fibers. One patient displayed scattered necrotic and regenerative fibers without inflammatory infiltrates. Most of the fibers presented an equal number of degenerative-regenerative alterations and no increase in fibers with internal nuclei. Oxidative histochemical analysis, ATP techniques, HLA as well as C5b9 staining were unremarkable. No signs of microvascular damage were detected.

Overall, muscle biopsies coupled with electrodiagnostic studies and imaging can be valuable tools in the multimodal assessment of SARS-CoV-2 patients with suspected myopathies.

Treatment

There are no specific treatments for SARS-CoV-2-associated myopathies. As a rule of thumb, inflammatory myopathies associated with SARS-CoV-2 infection should be treated with corticosteroids (e.g., intravenous methylprednisolone 1 g/die for 3-5 days followed by oral prednisone 1 mg/kg/die for 4 weeks with slow tapering)[11,25,70]. Although there is no high-quality evidence available, another report suggests the use of tocilizumab[25].

In the context of CIM, controlling risk factors and providing support therapies remain the mainstay of treatment. Avoiding hyperglycemia, certain drugs (vasoactive medications, corticosteroids, neuromuscular blocking agents, sedatives aminoglycosides, vancomycin), and limiting parenteral nutrition, as well as prolonged bed immobilization and mechanical ventilation reduce the risk of ICU-acquired CIM[71]. Intensive insulin therapy and early rehabilitation seem the most useful approaches for preventing CIM. There is no high-quality evidence supporting the use of corticosteroids or electric muscle stimulation in this setting[72].

Patients presenting with rhabdomyolysis are at increased risk for heme-induced acute kidney injury[73-75]. Early and aggressive fluid resuscitation is the major preventative measure. Patients presenting CK levels > 5,000 U/L or increasing values regardless of baseline values should receive intravenous fluids[76]. Isotonic fluids with an initial volume repletion at a rate of 1- 2 L/hour may be preferred over alternatives, such as colloids. There are some limited data to support the use of urine alkalinization with bicarbonate, loop diuretics, mannitol, and routine renal replacement therapy in severe rhabdomyolysis[76].

Take-home message

- Muscle involvement in the context of SARS-CoV-2 infection includes myalgia, myositis, rhabdomyolysis, as well as critical-illness myopathies[14].
- Rare SARS-CoV-2 cases with muscle involvement presented an inflammatory-like phenotype with some features of type I interferonopathies, a group of autoinflammatory disorders with prominent enhanced type I interferon signaling.
- Muscle MRI is valuable for assessing SARS-CoV-2-associated muscular changes, such as sarcopenia and cachexia in patients with prolonged weakness.
- Histopathological analysis of muscle biopsies from SARS-CoV-2 patients with muscle involvement may show inflammatory and/or chronic illness myopathy-related changes.
- There are no specific treatments for SARS-CoV-2-associated myopathies. Inflammatory-like forms should be treated similarly to inflammatory myositis, whereas critical illness myopathies require ICU-related risk factors to be controlled and the provision of support therapy.

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