Long-term Orthopedic Manifestations of COVID-19: Heterotopic Ossification and Digital Necrosis

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ABSTRACT

Despite its classification as an atypical pneumonia, COVID-19 is a disease that is capable of inflicting damage beyond the respiratory system. The wide range of musculoskeletal complications secondary to acute COVID-19 are a significant source of morbidity in hospitalized patients. We present the case of a 23-year-old woman with severe COVID-19 who required intubation and had a prolonged hospital course that was complicated by partial-thickness necrosis of her fingers and heterotopic ossification of the distal thigh. We review current treatments for these orthopedic conditions in the setting of SARS-CoV-2 infection as well as highlight areas for future research. Additionally, we discuss the subacute musculoskeletal complications of COVID-19, which are among the most common long-term manifestations of the disease and are increasingly important for a growing number of COVID-19 survivors.

KEYWORDS: COVID-19; orthopedic; heterotopic ossification; digital necrosis

INTRODUCTION

In late 2019, the first cases of the novel coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China.[1] Since then, the disease has become a worldwide pandemic resulting in hundreds of millions of cases and more than 6 million deaths.[2] Although initial attention focused primarily on the respiratory ramifications of the disease, COVID-19 is now recognized as a multi-system disease that can cause potentially devastating complications and long-term dysfunction throughout the body.

A variety of musculoskeletal complications related to both acute and post-acute sequelae of COVID-19 (PASC, also known as "Long COVID") have been reported.[3,4] These complications may in part be explained by the presence of angiotensin-converting enzyme 2 (ACE-2), the virus's major entry receptor, on skeletal muscle, synovial tissue, and the endothelium of small vessels.[5,6] Additionally, the widespread and prolonged inflammatory response as well as a prothrombotic state triggered by SARS-CoV-2 infection probably plays a role. We present a patient with severe COVID-19 who required intensive care unit (ICU) admission and mechanical ventilation. Her case was further complicated by heterotopic ossification of the distal thigh and digital necrosis. Additionally, we review other frequently reported musculoskeletal complications of COVID-19 illness and treatment both in the acute and subacute settings.

CASE REPORT

A 23-year-old-woman (unvaccinated against SARS-CoV-2) was admitted with shortness of breath and weakness due to COVID-19, after a normal vaginal delivery five days previously. A computed tomography angiogram (CTA) of her chest demonstrated pneumomediastinum, a segmental filling defect in the left lower pulmonary artery, and diffuse ground-glass opacities consistent with COVID-19 pneumonia. She was admitted to the intensive care unit and intubated for persistent respiratory distress. Her 81-day hospital course was complicated by refractory hypoxemia treated with venovenous extracorporeal membrane oxygenation (VV ECMO), pneumomediastinum, subsegmental pulmonary emboli, and disseminated intravascular coagulation managed with cryoprecipitate transfusions.

This patient also experienced orthopedic complications, and on hospital day 38 the Orthopedic Hand Service was consulted for partial thickness necrosis and dry eschars of the nail and dorsal fingertips distal to the distal interphalangeal joint (DIP) of the right index, middle, and ring fingers (**Figure 1a**). No acute findings were evident on plain radiographs (**Figures 2a-c**). The physical exam was limited due to the patient's intubated status. She had signals via Doppler ultrasound at the radial and ulnar arteries as well as her deep and superficial palmar arches. Her partial thickness digital necrosis was managed conservatively with therapeutic IV heparin and partial amputations were planned in the event of infections. Upon extubation, re-examination revealed that she had intact motor and sensory function of her right hand. The patient's skin findings continued to improve, with progressive resolution of the area of dry eschar (**Figure 1b**).

She was evaluated and followed by occupational therapy for upper extremity strength and range of motion (ROM) training and activities of daily living (ADL) training throughout her hospital course.

Figures 1a,b. Clinical photograph of dorsal right hand showing index, middle, and ring finger partial thickness necrosis at presentation (a), and clinical photograph of dorsal right hand 1 month later with interval improvement with conservative therapy and wound care (b).

Figures 2a-c. 3-view plain radiographs of right hand including anterior-posterior (AP) (a), oblique (b), and lateral (c) views, showing no acute fractures or bony pathology.

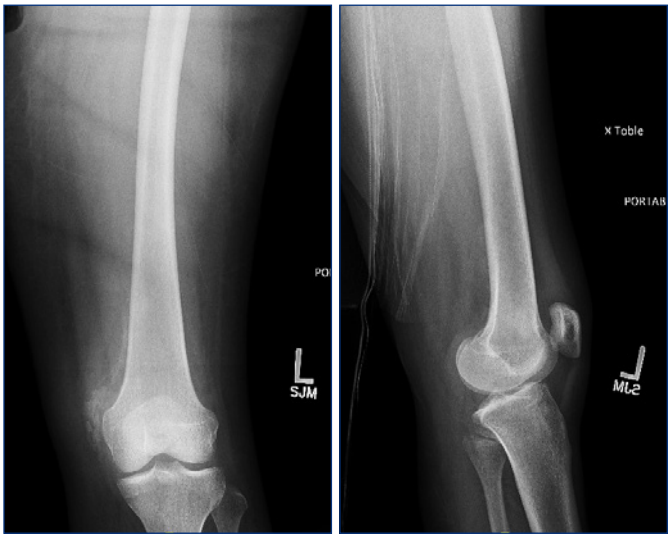
Several weeks after the appearance of her partial thickness digital necrosis, the Orthopedic Service was consulted for atraumatic left medial knee pain. She had a palpable, firm, non-fluctuant mass at the left distal medial thigh and both active and passive motion of the left knee were limited by pain. Radiographs and computed tomography (CT) scans demonstrated heterotopic ossification of the left vastus medialis (**Figures 3a,b; Figures 4a-c**). She was treated with nonsteroidal anti-inflammatories for pain control and physical therapy. She was seen by physical therapy throughout her hospital course for strength and range of motion (ROM) training as well as gait training, with nearly full resolution of her knee ROM. She was discharged to an acute rehabilitation center to facilitate recovery of her strength, flexibility, and functional independence. At two months after discharge, she had regained lower extremity strength and ROM, was able to ambulate with assisted devices, and had achieved independence with functional mobility.

DISCUSSION

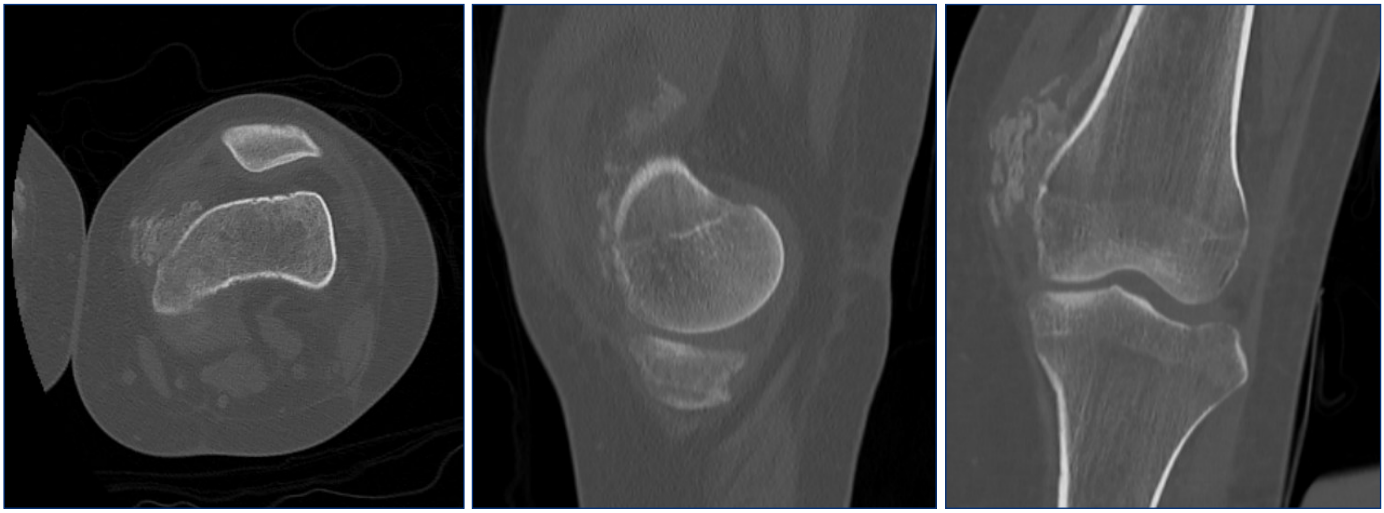
Early in the pandemic, COVID-19 was characterized as an atypical pneumonia, but it is better understood as a multi-system disease, as exemplified by our case of a 23-year-old woman with severe COVID-19 whose prolonged hospital course was complicated by heterotopic ossification and digital necrosis.

Endothelial dysfunction, inflammatory cytokine release, and hypoxia trigger decreased production and increased consumption of naturally occurring anticoagulants during severe

Figures 3a,b. Plain radiographs of distal femur with anterior-posterior (AP) (a) and oblique views (b), showing radio-opaque density suggestive of heterotopic ossification.



Figures 4a-c. Computed tomography (CT) scan of right distal femur with axial (a), sagittal (b), and coronal (c) views characterizing the extent of heterotopic ossification.



viral infection.[7] In COVID-19, direct endothelial injury from the SARS-CoV-2 virus via the ACE2 receptor may further exacerbate the coagulopathy.[8] The prothrombotic state can result in macrovascular as well as microvascular complications, such as the partial thickness digital necrosis seen in our patient.[7] Of note, digital necrosis is also well-described in patients requiring vasopressors and ICU-level care.[9,10] Thus, the exact etiology of acral necrosis in the setting of COVID-19 is likely multi-factorial and incompletely understood. Purpura, the cutaneous pattern that precedes digital gangrene in many of the reported cases, is characteristic of an occlusive micro-thrombotic process.[10,11] The preservation of major peripheral pulses in many cases also suggests a microvascular etiology.[9,12] Freeman et al analyzed six acral retiform purpura or necrotic lesions associated with COVID-19. The histopathology demonstrated non-inflammatory to pauci-inflammatory thrombi, leading the authors to conclude that acral necrosis is a cutaneous manifestation of the hypercoagulable state in COVID-19 patients.[10] However, poor responses to anticoagulation regimens have been reported in several cases of acral ischemia associated with COVID-19, prompting hypotheses that other processes such as neutrophil extracellular traps (NETs) or cold-sensitive antibody/immunoglobulin responses to the virus may play a role in the pathology.[12,13]

No standardized protocol exists for treatment for COVID-19-associated digital necrosis. The most common treatment reported in the literature is early and aggressive anticoagulation.[9,12] Further investigation is needed to determine if targeted immunotherapy or pharmaceutical agents dissolving NETs prove effective in treating digital ischemia unresponsive to anti-coagulation therapy. In the majority of reported digital necrosis cases, patients responded to conservative management, including wound care and anti-coagulation, or they died from other effects of COVID-19; however, Morales-Perez et al presented a case of surgical reconstruction of a necrotic thumb as well as a review of digital reconstruction in the setting of microvascular disease.[14]

In addition to digital necrosis, patients with severe COVID-19 are also at risk for heterotopic ossification (HO), a musculoskeletal complication characterized by ectopic formation of bone in soft tissues and around joints.[15,16] The exact mechanism of atraumatic HO remains unclear. It is thought to involve the differentiation of perivascular mesenchymal cells into osteoblasts when exposed to proinflammatory cytokines in the setting of altered local tissue factors, such as oxygen tension and pH.[16,17] In addition to the global inflammation experienced by COVID-19 patients, those requiring intubation are subject to prolonged

immobilization, another known risk factor for development of HO.[18,19] In fact, the reported cases of HO associated with COVID-19 have occurred exclusively in individuals who required mechanical ventilation.[20–24] In the largest series on the topic, Stoira et al retrospectively analyzed CT imaging of 52 intubated COVID-19 patients and found evidence of HO in ten (19%).[20]

Symptomatic HO presents most commonly as pain or loss of motion at a joint and has been reported around the hip, shoulder, or knee of COVID-19 patients requiring ICU level of care.[20–22] The diagnosis can be confirmed with radiographs; however, they have limited sensitivity early in the process.[17] Given the limited literature on HO with COVID-19 , treatment options are based on those utilized for HO secondary to neurologic insult or local trauma. NSAIDs, bisphosphonates, and radiation therapy are effective strategies to prevent HO in certain settings but no pharmaceutical treatment exists to address HO after it has formed.[17,18] NSAIDs can be utilized for prophylaxis and pain relief, but surgical removal remains the standard treatment when there is functional impairment and lack of improvement with conservative management including pain control and physical therapy.[17] The role of physical therapy in treating HO is a controversial topic. Historically, HO was considered a contraindication to range of motion exercises, based on the formation of ectopic bone in animal models subjected to aggressive stretching.[25,26] However, more recent research suggests that passive stretching may help preserve joint range of motion in patients with HO.[18,27] The optimal timing and types of physical therapy interventions have yet to be determined.

The musculoskeletal complications of COVID-19 are not limited to the acute effects of the disease and its treatment. In a long-term study of 285 patients, Karaarslan et al found that 40% of survivors had at least one musculoskeletal symptom six months post-infection, most commonly fatigue, joint pain, or myalgia.[4] A meta-analysis of persistent post-acute sequelae in more than 250,000 survivors found similar rates of muscle weakness.[28] Although critical illness myopathy is a well-documented consequence of ICU treatment for COVID-19 and other diseases, myopathic changes have also been documented in patients with mild COVID-19 infection, suggesting a different etiology in some cases.[29,30] Proposed mechanisms for post-acute muscle weakness include viral infiltration into skeletal muscle or muscle damage secondary to an aberrant immune response.[31] Physical activity has proven a powerful tool for preventing and improving myopathy associated with long-term COVID-19.[1,31] Rehabilitation should begin as soon as sedation and clinical stability allow; previous studies have demonstrated the feasibility and benefits of ambulation in ICU patients.[32] Post-hospitalization, recovering patients should partake in exercise that balances strength and flexibility to improve their gait as well as regain muscle mass.[1] Exercise programs proven effective in restoring function in randomized controlled trials involving SARS-CoV-1 survivors could serve as helpful templates for current efforts to develop rehabilitation protocols.[33] Recent studies have also explored the role of neuromuscular electrical stimulation and vitamin D supplementation in preserving and recovering muscle function, although further research is needed to determine the effectiveness of these modalities.[34,35]

Despite increasing availability of vaccines and treatments for COVID-19, hundreds of thousands of new infections occur daily.[2] Questions about the pathogenesis and optimal treatment for COVID-19-associated musculoskeletal conditions, especially long-term effects, require continued investigation. Increased understanding of the orthopedic manifestations of the disease is critical to improving care for patients and minimizing the healthcare burden.

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