

## Case Report

## A case report of a patient with COVID-19 infection and widespread heterotopic ossification

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### ABSTRACT

Since the beginning of the novel coronavirus disease-2019 (COVID-19) pandemic, physical medicine and rehabilitation specialists have played an important role in fighting this disease apart from the pulmonary rehabilitation. As a high number of patients have needed immobilization and intensive care unit (ICU) treatment, many complications have emerged inevitably. Heterotopic ossification (HO) is one of these complications. Herein, we present a case of young male patient who had widespread HO in his shoulders, elbows, and hips. Although he managed to survive, he still has difficulty in ambulation and daily living activities. Given the continuing high prevalence of COVID-19, many patients would need immobilization and ICU treatment. Therefore, causes of HO should be scrutinized, physicians and caregivers need to raise vigilance, and comprehensive protective measures should be put in place. On the other hand, as HO is used to be diagnosed quite frequently in the patients with neurological diseases, diagnosis of HO in the COVID-19 patients should not automatically be linked to the stay in the ICU. Yet, it is a fact that impaired immune response is prevalent both in COVID-19 and HO. The correlation between COVID-19 and HO is remarkable, but further research is needed to establish a causal relationship.

**Keywords:** COVID-19, heterotopic ossification, immobilization.

The novel coronavirus 2019 disease (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first emerged on December 31<sup>st</sup>, 2019 in Wuhan, China. On March 11<sup>th</sup>, 2020, the World Health Organization (WHO) declared SARS-CoV-2 outbreak as a global pandemic. Since its discovery, COVID-19 has caused staggering death toll, more than three million as of April 2021, overwhelmed healthcare systems, and impacted economies and communities all around the world. Patients infected with COVID-19 have a broad range of presentations: about one-fifth of infected patients experienced no symptoms, while symptomatic patients usually have fever, cough fatigue and, albeit less frequently, loss of taste or smell, headache, muscle pain or joint pain, diarrhea and sore throat.<sup>[1]</sup> Fortunately, about

80% of the symptomatic patients recovered from the disease without resorting to hospital treatment, whereas hospitalization and oxygen support were required for 15% of them and a remaining 5% needed intensive care treatment. Acute respiratory distress syndrome (ARDS) and respiratory failure are found to be the leading causes of deaths. Thromboembolic complications, secondary infections, sepsis and septic shocks, and multi-organ failures can also be present in severely ill COVID-19 patients. There still exist no effective method of treatment in fighting this disease. In mild cases, symptomatic treatment and bed rest is usually recommended. While there is no approved antiviral regimen, already existing drugs such as lopinavir/ritonavir, remdesivir, favipiravir, chloroquine, hydroxychloroquine, and tocilizumab has

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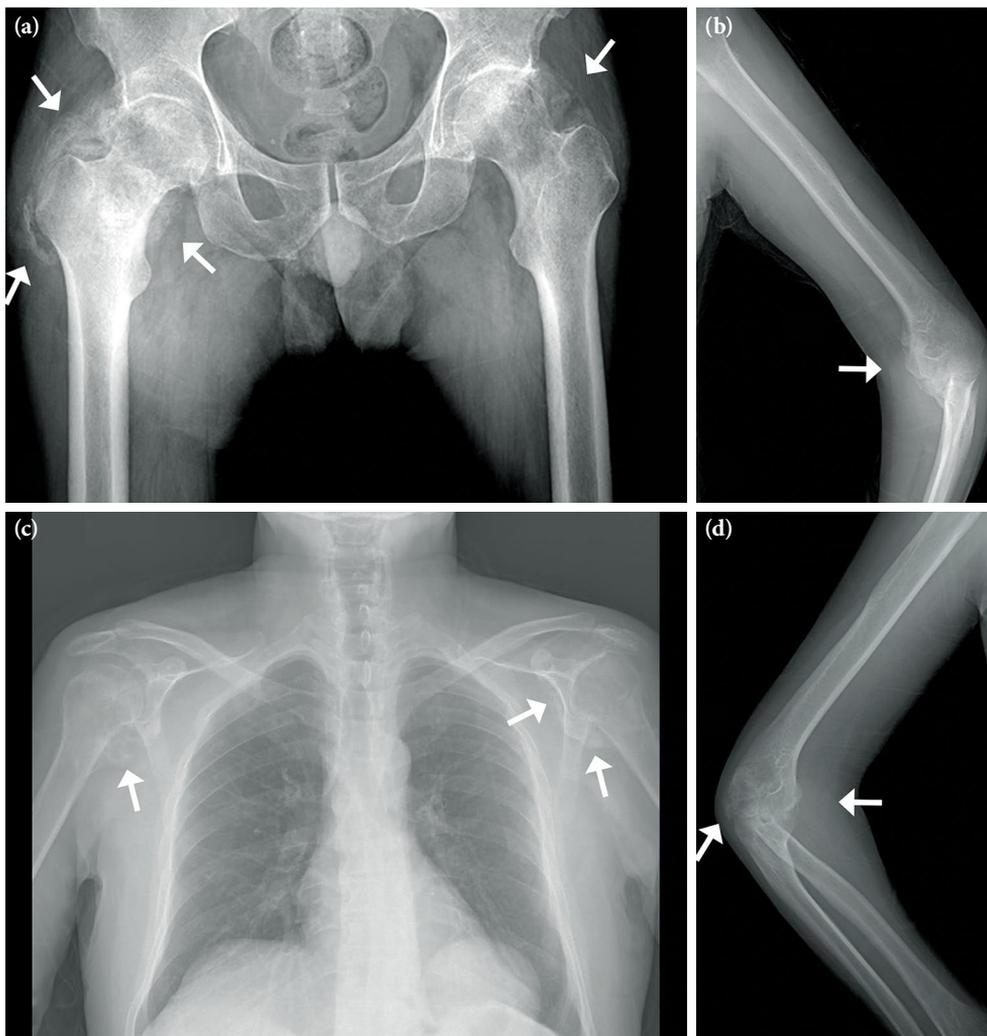
been used on case-by-cases basis. Vitamin C, D, and zinc have been recommended as an adjunctive therapy. Yet, in severe patients, oxygen support, hospitalization and immobilization are crucial for management of the illness. In case of respiratory failure, mechanical ventilation and, in septic shock, hemodynamic support are vitally important, as well.<sup>[2]</sup>

Heterotopic ossification (HO) is the abnormal mature lamellar bone formation in the soft tissue which is usually present in patients with peripheral and central nervous system lesions. It is diagnosed in 20 to 29% of the patients with spinal cord injuries (SCIs) and 5 to 20% of those experiencing traumatic

brain injuries (TBIs).<sup>[3]</sup> Traumas, severe burns, fractures, and joint replacement surgeries are the other potential causes of HO. In general, HO occurs in periarticular, most frequently at hip, elbow, knee and shoulder.<sup>[4]</sup> In this report, we present an atypical presentation of HO in a patient with SARS-CoV-2 infection.

### CASE REPORT

A 45-year-old male with severe COVID-19 symptoms and presence of a ground-glass pattern on thoracic computed tomography (CT) was admitted to a hospital at the beginning of April 2020. He had a



**Figure 1.** (a) Pelvic radiograph, anteroposterior view, the radiograph showing varying-sized ossified shadows over the anterolateral periarticular area of the left hip joint and around the right hip; (b) Right elbow radiograph showing medial ectopic ossification; (c) Anteroposterior chest radiograph, taken one month after ICU discharge showing HO bilaterally around shoulders; (d) Left elbow radiograph showing ossification around the elbow.

ICU: Intensive care unit; HO: Heterotopic ossification.

history of hypertension, but no underlying respiratory or neurological pathology. His nasopharyngeal swab test concluded positive for ribonucleic acid and oseltamivir, hydroxychloroquine, and broad-spectrum antibiotics were started immediately. On the second day of the treatment, he required mechanical ventilation. Therefore, he was transferred to intensive care unit (ICU) where he underwent endotracheal intubation and favipiravir was added to his treatment. A rehabilitation program was planned for passive range of motion (ROM) exercises, but could not be implanted due to ARDS and complications. Bed positioning for every 2 h and prone position 12 to 16 h for supporting oxygenation were performed continuously. During his ICU period, he developed sepsis and his broad-spectrum antibiotherapy was continued. After one month, tracheostomy was performed. He stayed two months in the ICU and he stated on mechanical ventilator for 55 days. When the patient was taken to the ward from the ICU, there was still a need for oxygen support. He stayed eight more days in the ward. After clinical stability was ensured, rehabilitation program was planned for improve the ROM and functionality. Following discharge, the patient was called to the physical medicine and rehabilitation (PMR) outpatient clinic for further evaluation. One week later, he visited the outpatient clinic with complaints of walking disability and stiffness in both hips, elbows, and shoulders. The patient was unable to stand up and move comfortably, since he left the ICU. He was completely dependent on daily living activities.

During the physical examination, no red, warm and swollen joint was detected. He had pain in his elbows and hips bilaterally. Hard and fixed growth masses were palpated in his both hips. He had total ankylosis of both right and left elbow at 45 and 50 degrees of flexion, respectively. Besides, the ROM in the right and left shoulders decreased to 0 to 80 and 0 to 90 degrees of flexion, 0 to 60 and 0 to 70 degrees of abduction and 0 to 20 and 0 to 30 degrees of internal rotation, respectively. Flexion deformity was observed on his both hips at 10 degrees in the left and 20 degrees in the right side. He had difficulty in lying in the prone position. The ROM was detected as normal on the other joints. His muscle strength could not be evaluated in the affected limbs accurately in regard to motion disability. The X-rays of all affected joints revealed HO in hips, shoulders, and elbows (Figure 1). Meanwhile, the laboratory test results showed increased alkaline phosphatase (ALP) (291 IU/L) and normal serum calcium (9.3 mEq/L)

levels, as well. Chronic sensory-motor polyneuropathy was determined in electroneuromyographic (ENMG) studies in all four limbs and it was compatible with the critical illness neuropathy. For further investigation, the patient had a cranial magnetic resonance imaging (MRI) which showed mild cerebral atrophy with no other vascular or demyelinating lesions.

A home-based rehabilitation program was planned to improve the ROM, muscle strength, and functionality. The program consisted of slight stretching exercises, submaximal muscle strengthening exercises, and pulmonary exercises. A physiotherapist supervised him throughout this program. A written informed consent was obtained from the patient.

## DISCUSSION

Recently, Meyer et al.<sup>[5]</sup> examined a case series of four COVID-19 patients complicated with HO. According to the study, those were the first known COVID-19 cases exhibiting such complications. In that case series, all patients had only one joint impacted by HO. Later on, Ploegmakers et al.<sup>[6]</sup> published case report of two COVID-19 cases presented with widespread HO. The current case is another reported case of a severe COVID-19 patient with presentation of widespread HO in bilateral hips, elbows, and shoulders. Two similarities between the patients of Ploegmakers and ours are striking. The first is that all patients suffered from severe COVID-19 and all of them needed long-term mechanical ventilation and hospitalization in the ICU. Second, HO emerged in both hips, shoulders, and elbows in all three of patients.

Many reasons can contribute HO to occur in COVID-19 patients, such as long-term immobilization, high burden of inflammation, long-term dependence of mechanical ventilation and critical illness polyneuropathy. Also, COVID-19 and HO occurrence may not be directly associated; however, the need for further studies to fully establish a causal relationship between HO and COVID-19 is evident. In particular, the fact that the joints affected by the widespread HO in the Ploegmakers' case and in our case are the same supports the need to investigate this causal relationship.

Heterotopic ossification usually emerges in patients with peripheral or central nervous system pathologies in the TBI and SCI populations. Besides, spasticity, prolonged loss of consciousness, and long bone fractures significantly increase the

risk of developing HO.<sup>[7]</sup> Traumas, severe burns, fractures, Guillain-Barre syndrome (GBS) and joint replacement surgeries are the other possible causes of that illness.<sup>[8]</sup>

Heterotopic ossification leads to pain in the joint, decreased ROM, and even ankylosis in some cases. In the involved region, redness and warmth can be observed up to 12 weeks.<sup>[9]</sup> Heterotopic ossification impairs patient's daily living activities and has a dramatic effect on quality of life. In early stages, bone scintigraphy and ultrasonography can provide early diagnosis paving the way for acute treatment. After six months, however, bony maturation usually occurs and HO rarely regresses.<sup>[10]</sup> Plain radiography can detect HO after one to two months. Computed tomography provides us with a better visualization by elucidating the localization and anatomical vasculatures around the HO. Additionally, in laboratory investigation, it may reveal temporary low calcium levels and elevated ALP levels. The 24-h urine prostaglandin E2 (PGE2) levels may be elevated.<sup>[4]</sup> In the current case, ALP levels were (56 IU/L) normal at the time of hospital admission and gradually increased during the hospitalization in the ICU, and it peaked (291 IU/L), when he visited the PMR outpatient clinic and, then, tended to decrease. There were no PGE2 levels.

Although the exact pathology of HO still remains unclear, it is highly associated with the underlying inflammatory process and macrophage activity.<sup>[11]</sup> Cytokines and metabolic initiators of HO can be released as a result of unregulated immune system or inflammatory response.<sup>[12]</sup> Also, SARS-CoV-2 infection is known to have caused inflammation and dysregulation in the immune system and have modulated macrophage-mediated events.<sup>[12]</sup> As seen in the recent case series and in our case, the fact that HO presented in the patients who suffered from severe COVID-19 infection undergoing mechanical ventilation in the ICU supports the hypothesis that high levels of inflammation in the body may have caused HO.<sup>[4,6]</sup> In a case report, three previously healthy individuals developed HO associated with catastrophic non-traumatic respiratory illness requiring cardiorespiratory support.<sup>[13]</sup>

Moreover, studies confirm that COVID-19 has neuroinvasive properties. Its exact mechanism is yet to be known, but it is considered to be responsible for macrophage associated transmission of blood-brain barrier, trans-synaptic transmission, and olfactory epithelium invasion.<sup>[14,15]</sup>

Although HO mostly occurs in TBI and SCI patients, there have been numerous cases of various neurological disorders such as GBS, critical illness myopathy and neuropathy and stroke that have been complicated with HO. Zeilig et al.<sup>[16]</sup> screened 44 patients with critical illness polyneuropathy and HO developed in seven of them. However, in this study, it was not reported what the underlying disease caused critical illness neuropathy in patients with HO.

In addition, Zeilig et al.<sup>[16]</sup> reported that HO occurred only in patients with GBS who experienced prolonged hospitalization and underwent ventilation. As was the case in the Meyer's study,<sup>[4]</sup> our case stayed in the ICU for a prolonged period requiring mechanical ventilation support. Therefore, it is likely that dysregulation in the acid-base homeostasis during the mechanical ventilatory period might have triggered HO. Metabolic alkalosis has an impact on bone metabolism. It increases osteoblastic enzyme activity and decreases the osteoclastic enzyme activity.<sup>[18]</sup>

Heterotopic ossification may also be related to some genetic predispositions. This may be the reason why not all of the patients with head traumas develop HO. Limb spasticity and prolonged immobilization are also among the risk factors for HO.<sup>[16]</sup> Our case stayed 60 days in the ICU, whereas the longest ICU stay was 30 days in the Meyer et al.'s report.<sup>[5]</sup>

Treatment of HO involves a combination of methods including physiotherapy, medical management, and radiotherapy. When bony transformation occurs, surgical excision is usually needed. Medical treatment primarily aims to prevent HO. Non-steroidal anti-inflammatory drugs and bisphosphonates have been proved to be helpful in its treatment. Radiotherapy has been successfully used in after hip arthroplasty for prevention of HO.<sup>[19]</sup> However, it is difficult to use radiotherapy in patients with brain trauma, as we usually cannot predict HO location. In the current case, we recommended indomethacin 25 mg t.i.d. and a rehabilitation program. The follow-up and rehabilitation process of the patient is still ongoing.

In conclusion, HO can substantially impair patient's daily routines. Limitations in the ROM of joints lead to difficulty in walking, sitting, eating, or dressing. Once it emerges in patients, it is difficult to treat. It is usually diagnosed as a complication in patients with severe COVID-19 who experience prolonged immobility and receive ventilation. Although HO has often been associated with trauma

or neurological diseases, it can be also seen in patients with critical illness neuropathy. Widespread HO in a previously completely healthy young male patient may be related to COVID-19 infection due to similar pathogenesis or may be related to prolonged ICU stay due to infection. Yet, it should be considered that there may also be mechanisms between COVID-19 and HO that have still stayed uncovered. The presence of a painful, red, swollen joint, and elevated ALP levels should be scrutinized carefully. Yet, medical imaging must be performed to the affected joints to make a definitive diagnosis. Early consultation with a PMR physician is crucially important in fighting against this illness. The ROM exercises should be recommended for all patients during and after the ICU treatment. After discharge, all patients should be informed to be alert on symptoms of HO and should be examined by a PMR physician, if they show any symptoms. Timely intervention provides us with ease in medical management of the illness and reduces HO progression, thereby preserving the joint function. Given the pressing prevalence of COVID-19, it is safe to assume that in the period ahead there would be more and more patients needing ICU treatment and, therefore, facing the risk of HO. To avoid potential impairments caused by HO, early diagnosis and intervention is the key. Nonetheless, there is still need for further studies to fully establish a causal relationship between HO and COVID-19.

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