

The Unrecognized Orthopedic Burden of COVID-19: Heterotopic Ossification of the Hip Joint

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COVID-19 has extensively affected the health-care organization with varying impact on different medical specialties. Long term ICU admission is associated with a less familiar complication: the formation of heterotopic ossifications (HO). In this case report we would like to emphasize the unrecognized burden of the coronavirus pandemic in patient care from the perspective of the orthopedic surgeon. We describe two patients with major HOs around their hip joints after COVID-19. Current literature underlines the increased prevalence of HO formation in COVID-19 patients requiring long-lasting mechanical ventilation and ICU admission including prone positioning. Preventing HO formation remains a difficult undertaking without obvious evidence supporting a golden standard treatment. We advice early passive mobilization during ICU stay, also during prone positioning, serum ALP follow-up during admission, NSAID administration if possible and a low threshold in the use of radiotherapy of joints with a limited range of motion.

INTRODUCTION

The world was struck by a devastating disease originating from Wuhan, China in December 2019. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to a pandemic with 500 million infections and more than 6 million deaths, making it one of the deadliest viruses in history¹. Intensive care unit (ICU) admission was necessary for 3-4% of all patients and usually long-term ventilation was inevitable². Invasive mechanical ventilation in prone position was the only technique that demonstrated to increase the survival in patients with severe acute respiratory distress syndrome (ARDS) due to COVID-19³.

COVID-19 has extensively affected the health-care organization with varying impact on different medical specialties. At one-year post ICU admission, more than half of those patients experience problems, such as reduced condition, shortness of breath, and muscle weakness and soreness⁴. Long term ICU admission is by itself also associated with a less familiar complication: the formation of heterotopic ossifications (O)⁵. The abnormal formation of mature lamellar bone in soft tissues without connection to the periosteum is mostly seen, around shoulders, elbows, hips and knees. Its formation is associated with paralysis and

immobilization following trauma, neurologic injury, ARDS, musculoskeletal surgery and severe burns⁶. Major HOs might result in swelling, local temperature increase and erythema but especially in articular pain, joint ankylosis and decreased articular function⁷.

In this case report we would like to emphasize the unrecognized burden of the coronavirus pandemic in patient care from the perspective of the orthopedic surgeon. The past years several patients presented to the orthopedic outpatient clinic with HOs around their hip joints following long-term ICU stay. We describe two patients with major HOs around their hip joints after COVID-19. Both patients gave informed consent for publication.

CASE 1

A male in his mid-70s known with pulmonary hypertension, hypercholesterolemia, and polyneuropathy, was admitted to the ICU with respiratory failure due to a severe COVID-19 pneumonitis. He was ventilated for 10 weeks, including 2 weeks of prone position for 2 weeks. His ICU admission was complicated with, among other things, an intramuscular hamstring hemorrhage due to antithrombotic therapy for a peripheral pulmonary embolus.

After 10 months of (pulmonary) rehabilitation the patient attended the orthopaedic outpatient clinic with severe pain and a decreased range of motion of the left hip. Physical examination showed marked atrophy of all extremities. The left hip was ankylosed in 30° of flexion.

Radiological imaging showed mild signs of hip osteoarthritis. Extensive periarticular ossifications of the left hip with a femoral-acetabular osseous bar (Brooker Grade IV) were seen (Figure 1). An additional CT-scan showed the periarticular ossification in the course of the iliopsoas muscle. In addition, ossifications were seen in the pectineus-, gemellus superior-, piriformis- and external obturator muscles (Figure 2).

A Smith-Petersen approach was utilised to resect the anterior femoral-acetabular osseous bar which was

thought to be the main problem for the patient. The anterior joint capsule was left intact. After resection of the bony bar, the range of motion was tested and showed 90° flexion, maximal extension and 30° of internal and external rotation. The postoperative course was uncomplicated.

CASE 2

A man in his late 70s known with hypertension, and prostate cancer (which was treated with brachytherapy) was admitted to the ICU with respiratory failure due to a severe COVID-19 pneumonitis. He was ventilated for 6 weeks of which in prone position for less than a week. Eleven months after his ICU admission the patient attended the



Fig. 1 — AP-Pelvis X-ray (Case 1) showed extensive periarticular ossifications of the left hip.

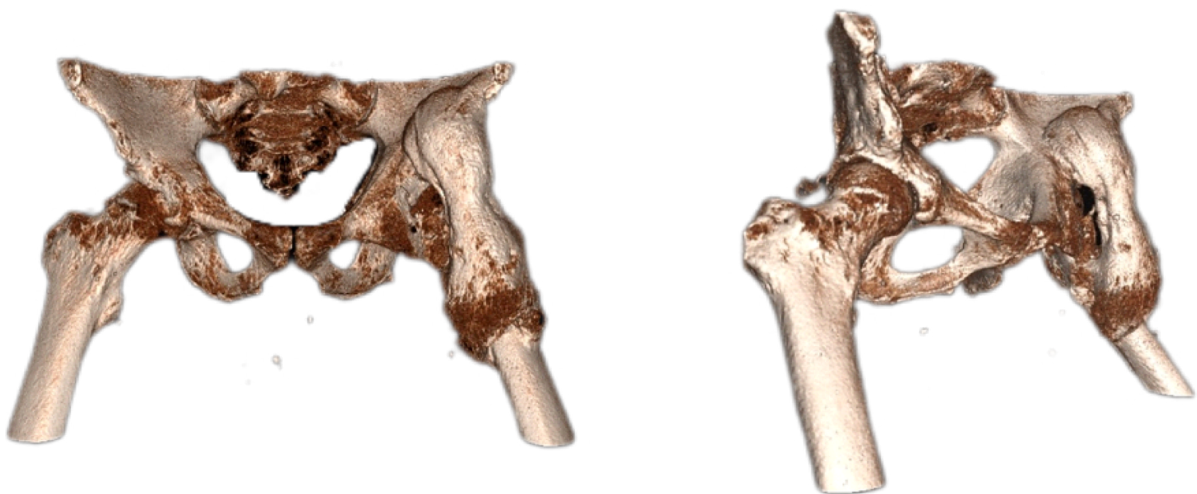


Fig. 2 — CT-scan (Case 1) showed the extensive periarticular ossification of the left hip. (left: anterior view; right: 45° oblique view).

orthopaedic outpatient clinic with severe pain and decreased range of motion of the left hip. Physical examination showed a fixed flexion contracture of 20°, but ability to flex up to 90°. No internal or external rotations and adduction or abduction were possible. Neurovascular evaluation showed a footdrop on the ipsilateral side. Electromyography showed axonal sensorimotor polyneuropathy due to critical illness polyneuropathy, commonly seen in COVID-19 patients^{8,9}. The examination of the contralateral hip was unremarkable.

Radiological imaging showed mild signs of hip osteoarthritis. Ossifications were noted on the posterior aspect of the left hip (Brooker Stage IV) (Figure 3). An additional CT-scan showed extensive periarticular ossifications posterior of the left hip following the course of the gluteus muscles, both the medius and minimus (Figure 4).

A classic posterolateral approach was used to reveal the HO. Both the insertion of the gluteus medius on the greater trochanter and the hip capsule remained intact. The ossification was grown around the sciatic nerve. The bony bar was resected step by step and the sciatic nerve was decompressed by the neurosurgeon. After resection, range of motion testing showed satisfactory results. The postoperative course was uncomplicated, yet the patient still suffered from a footdrop.

For both cases we chose to resect the HOs without replacing the hip joint because the patients did not experience hip pain prior to their ICU admission. The radiographic analysis showed only mild signs of osteoarthritis, which is common at this age. Their long ICU admission, severe deteriorated condition and HOs might result in a non-favorable outcome after total hip replacement with respect to instability (due to abductor insufficiency) and increase in prosthetic



Fig. 3 — AP-Pelvis X-ray (Case II) showed an extensive periarticular ossification of the left hip.

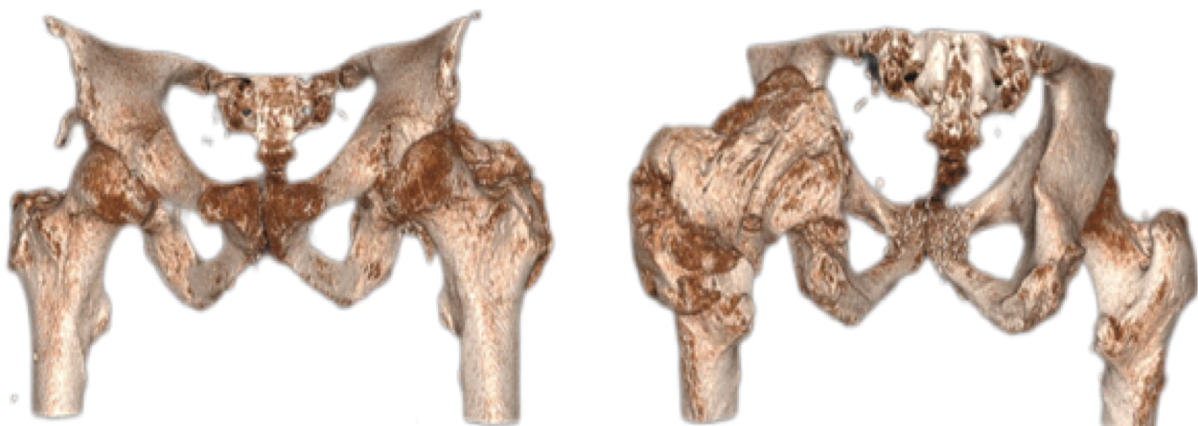


Fig. 4 — CT-scans (Case II) showed extensive periarticular ossifications of the left hip. (left: anterior view; right: posterior view).

joint infection as a result of dead-space. Replacing a non-symptomatic hip, which was expected, with only mild signs of osteoarthritis did not seem to be a beneficial treatment for these specific patients.

DISCUSSION

The current report describes two patients with an extensive HO of the hip joint. It emphasizes that HO should be considered in patients with articular pain and a history of COVID-19 infection with prolonged immobilization due to long-term ICU admission. However, the current literature is still scarce with respect to this entity.

Long-term side effects in COVID-19 survivors are common (80%, range: 65–92%), with 19% (range: 7–34%) originating from joints¹⁰. The prevalence of HO in COVID-19 patients seems to be about a fourfold higher than reported in patients with ARDS (5%)⁷. In patients with a spinal cord injury (SCI) the incidence of HO has been estimated to be between 10%–53%¹¹. The incidence of HOs as a complication after long-term ICU stay due to COVID-19 has not been described before. A literature search showed 12 case reports, reporting on 17 patients since November 2020^{6,12–22}. The current study excluded the case-report by Grgurevic et al. who reported on HO formation as a result of post-COVID exacerbations in fibrodysplasia ossificans progressiva. The patient was treated as an outpatient for her COVID infection²³. In addition, de l'Escalopier et al. reported on 4 post-COVID HO-cases, but the description was too little to add this to our literature search²⁴.

Most of the found cases reported on males (13, 76%), with only 3 reports on females (18%) and one (6%) case with an unknown gender. Their mean age was 52.9 ± 16.3 years [range 20 – 76]. All patients were admitted to the ICU for mechanical ventilation, with at least 9 ($\geq 53\%$) of the patients in prone position. The mean total time of admission [range 30 – 134 days], mechanical ventilation [22 – 70 days] and prone position could not be determined due to incompleteness of the case reports. NHOs were mainly found in the shoulders (N=17, 38%) and hips (N=19, 42%). Formation of HOs in SCI patients occurs predominantly around the hips (up to 97%) and is less common in the shoulder and knee and almost never seen in wrists, hands, ankles and feet²⁵.

Stoira et al. reported on five symptomatic and five asymptomatic patients (case-series) with a HO around the shoulder, the elbow and the hip after a severe COVID-19 infection requiring prolonged mechanical

ventilation⁷. Their median age was 71 years (IQR 67–74) with a median duration of mechanical ventilation for 36 days (IQR 25–45). Eight of the ten patients were in prone positioning during a median of 12 days (IQR 7–16). Neuromuscular blockade was used in 9/10 patients. A multivariate analysis showed that longer mechanical ventilation (OR 2.64 for each additional week) and longer hospitalization (OR 2.10 for each additional week) were significant risk factors for development of HO. The authors suggest that prolonged immobilization might have a crucial role in the occurrence of HO²⁶. In comparison to the case-reports and Stoira's case-series, the patients in the current study were a bit older (mid to late 70s), quite long on mechanical ventilation (respectively 70 and 42 days) and were also positioned prone for a certain amount of time (1–2 weeks). Neuromuscular blockade, with rocuronium, was used in at least one of the presented cases.

The pathophysiology of HO formation remains unclear^{27–29}. In recent years, correlations between HO formation and triggering factors and progenitor cells' differentiation into cartilage and bone, were studied¹¹. Mezghani et al. performed a retrospective single centre study in 19 of their HO patients after a severe COVID-19 infection who required ICU admission and mechanical ventilation. They found that only one had a significant demineralization (N=1; 5%) compared to 14% found in the literature²⁷. A possible explanation could be the shorter duration of evolution of HO in patients with COVID-19 (27). Systemic inflammation was seen in patient with COVID-19, which subsequently might increase the risk of HO²⁴. However, no association was found between the level of C-reactive protein (CRP) as a marker of systemic inflammation, and the risk of formation of HO in COVID-19 patients⁷. The current literature review showed that in at least 10/17 ($\geq 59\%$) patients an increase in serum alkaline phosphatase (ALP) was found during their ICU admission. The peak of serum ALP in literature was found after 10 weeks¹¹. In a retrospective study in individuals (total n=299, HO-development in n=19(6.4%)) with a spinal cord injury a significant correlation was found between abnormal ALP levels and HO appearance ($P < 0.001$). In addition, a normal level ALP and oral alendronate (ALN) intake was also found to be significant correlated, suggesting that ALN may play a role in preventing HO³⁰.

The only effective treatment option when HOs are formed is surgical removal of the ossifications, especially in HOs resulting in ankylosis and limitation

in joint mobility³¹. Surgical removal is potentially difficult and can only take place once the ossification has sufficiently mineralised ('mature'), with the risk of reoccurrence³². Preventing the need for surgery would be ideal. However, early recognition of HOs is difficult, especially in sedated patients³³. Localized pain, tenderness and swelling are symptoms in the early stage of HO. A restricted range of motion and soft tissue stiffness is found in later stages³⁴. Preventive measures such as the use of non-steroidal anti-inflammatory drugs (NSAIDs) and radiotherapy have not been studied in HO formation after COVID-19. NSAIDs are used successfully to prevent HO formation in patients after total hip arthroplasty (THA) and might be beneficial in SCI patients^{11,35,36}. The side-effects of NSAIDs (gastrointestinal, cardiovascular) and the interactions with other medication do not make it the ideal treatment for all patients. A single-dose radiation therapy a few days after diagnosing HO formation of the hips in patients with SCI showed promising results, with low numbers of HO relapse (5.3%)³⁷. It seems that radiologic improvement is unlikely after radiotherapy, but promising results concerning pain relief and range of motion improvements are reported³⁸. However, the use of radiotherapy as a prophylactic therapy is not a likely option in COVID-19 due to the systemic inflammation which cannot be treated with radiotherapy of a single joint and the additional costs and equipment^{38,39}. Also, the long-term side effects are unknown³⁷.

Other treatments include the use of bisphosphonates, BMP-inhibitors, Noggin (a TGF- β protein), transforming growth factor beta (TGF- β), retinoic acid agonists-RAR γ , rapamycin- Inhibitor of hypoxia-inducible factor 1a-(HIF1a), free radical scavengers and immune therapy with Imatinib¹¹. However, these novel treatments need additional clinical trials to show the profit in preventing HO formation.

The current cases and literature search suggest that long lasting mechanical ventilation including prone position, and the duration of hospitalisation are risk factors for formation of HOs in COVID-19 patients. However, a more severe COVID-19 infection and ARDS is obviously correlated with long lasting mechanical ventilation and hospitalisation. The two patients in the current report and at least 9 of the 17 ($\geq 53\%$) reported case patients in literature were in prone position for a period. Physical therapy protocols to improve range of motion and limit contractures during ICU admission have been recommended and are common practice⁴⁰. One could imagine the difficulties of passive mobilization in prone position,

especially of the shoulder and hip joints. In contrast, no predominance of anterior muscle involvement was found by Mezghani et al. In 10 patients with 19 HOs, 6 (31%) were found anterior and 6 (31%) both anterior and posterior²⁷.

CONCLUSION

Long term ICU admission due to COVID-19 is a risk factor for the formation of HOs. Current literature underlines the increased prevalence of HO formation in COVID-19 patients requiring long-lasting mechanical ventilation and ICU admission including prone positioning. Preventing HO formation remains a difficult undertaking without obvious evidence supporting a golden standard treatment. Due to the limited number of cases reported in literature we were unable to show potential correlations of clinical benefit, and we were only able to discuss potential associations. We advice early passive mobilization during ICU stay, also during prone positioning, serum ALP follow-up during admission, NSAID administration if possible and a low threshold in the use of radiotherapy of joints with a limited range of motion.

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