

Heterotopic Ossification in COVID-19: An Association Not Yet Documented? Two-case report

Osificación heterotópica en COVID-19, ¿la asociación aún no documentada? Reporte de dos casos

Aren, Leandro¹ , Mayer, Germán F.¹ , Hernández, Julián²

Received: 02/01/2023

Accepted: 07/25/2023

Correspondence

Leandro Aren. E-mail: leann.mdp@gmail.com

ABSTRACT

Heterotopic ossification (HO) is defined as the formation of bone tissue in areas of soft tissue where there is usually no bone. It is a rare/underdiagnosed disease usually related to paralysis and immobilization during the critical course of trauma, neurological lesions, acute respiratory distress syndrome (ARDS), surgery, or major burns. In the course of the SARS-CoV2 pandemic (new COVID-19), cases of critically ill patients with HO were reported; it is considered that the magnitude of the inflammatory reaction, a possible effect of the virus itself, and long periods of immobilization while the critical stage was taking place could be the determinants of this clinical entity.

During the hospitalization period of the cases described below, the occupational rate was 166 % and 200 %, and the workload of the nursing staff, measured by TISS-28 (Therapeutic Intervention Score System), was 72 points, nearly double the workload manageable by a nurse. At the same time, motor rehabilitation by the kinesiology team was postponed due to the need to address urgent circumstances such as optimization of ventilatory support and participation in maneuvers for changing the decubitus position. In this way, we interpret that the great work overload that occurred during the pandemic conditioned an inadequate provision of early mobilization, resulting in a higher prevalence of HO in severe post-COVID patients when compared with ARDS from other causes. We present two cases of HO in patients who underwent ARDS due to SARS-CoV2 at times of high workload.

Case 1: 48-year-old man, who was admitted to the ICU (Intensive Care Unit) due to severe community-acquired pneumonia (CAP) caused by COVID-19. History of obesity. The patient required 31 days of mechanical ventilatory assistance (MVA), 4 prone positioning cycles (192 hours in total), tracheostomy (TQT) on day 18, 23 days of neuromuscular blockers and 24 days of sedation. Active-assisted motion began on day 24 with a Medical Research Council (MRC) score of 38/60. A total of 52 days of hospitalization. Six months after discharge, the patient was diagnosed with bilateral HO of the hip.

Case 2: 58-year-old patient, admitted to the ICU with severe CAP caused by COVID-19. History of hypertension and obesity. The patient required 39 days of MVA, two prone positioning cycles (60 hours in total), TQT on day 7. A total of 45 days in the ICU and 111 in the hospital. One year after discharge, the patient was diagnosed with bilateral HO of the hip.

Key words: COVID-19; Ossification, Heterotopic

¹ Kinesiology Service, Intensive Care Unit. Hospital Madre Catalina Rodríguez. Merlo, San Luis

² Intensive Care Unit. Hospital Madre Catalina Rodríguez. Merlo, San Luis

RESUMEN

Se define como osificación heterotópica (OH) a la formación de tejido óseo en zonas de tejido blando en donde habitualmente no hay hueso. Se trata de una patología rara/subdiagnosticada habitualmente relacionada con parálisis e inmovilización durante el curso crítico de traumatismos, lesiones neurológicas, síndrome de dificultad respiratoria aguda (SDRA), cirugías o grandes quemados. En el transcurso de la pandemia por SARS-CoV2 (nuevo COVID-19) se reportaron casos de pacientes críticos con OH interpretándose que la magnitud de la reacción inflamatoria, posible efecto propio del virus, y largos periodos de inmovilización mientras transcurría la etapa crítica podrían ser los determinantes de esta entidad clínica.

Durante el período de internación de los casos que describiremos a continuación, el porcentaje ocupacional fue de 166 % y 200 % y la carga laboral del personal de enfermería, medida por TISS-28, fue de 72 puntos, excediéndose casi al doble de las posibilidades laborales. Al mismo tiempo la rehabilitación motora, por parte del equipo de kinesiología, se vio postergada ante la necesidad de atender circunstancias urgentes como la optimización del soporte ventilatorio y la participación en maniobras de cambios de decúbito. De este modo interpretamos que la gran sobrecarga laboral acontecida durante la pandemia condicionó una inadecuada provisión de movilización temprana dando como resultado una mayor prevalencia de OH en pacientes post COVID grave cuando se la compara con SDRA por otras causas.

Presentamos dos casos de OH en pacientes que cursaron SDRA por SARS-CoV2 en momentos de alta carga laboral.

Caso 1: Paciente masculino de 48 años, que ingresó a la UCI por NAC grave por COVID-19. Antecedentes de obesidad. Requirió 31 días de AVM, 4 ciclos de posición prona (192 hs total), TQT al día 18, 23 días de Bloqueantes neuromusculares y 24 de sedación. Comienza la movilización activa-asistida al día 24 con MRC 38/60. Un total de 52 días de Internación. A los 6 meses del alta se diagnosticó OH bilateral de cadera.

Caso 2: Paciente de 58 años, que ingresa a UCI por NAC grave por COVID-19. Antecedentes de HTA y Obesidad. Requirió 39 días de AVM, dos ciclos de posición prona (60 hs total), TQT al día 7. Un total de 45 días de UCI y 111 de hospital. Al año del alta se diagnostica OH bilateral de cadera.

Palabras clave: COVID-19; Osificación Heterópica

INTRODUCTION

The SARS-CoV 2 pandemic challenged the majority of the healthcare systems worldwide, with a high utilization rate of critical care and not enough qualified human resources. This situation generated the need to meet the demand by employing personnel without the necessary expertise or by increasing the workload of the staff in those areas. In this context, new publications emerge daily on the stress experienced by the healthcare system and personnel.¹

Patients who suffered from severe COVID-19 experienced prolonged stays in the ICU, prolonged use of analgesedative and neuromuscular blocking agents, the need for mechanical ventilatory assis-

tance (MVA), and extended prone positioning cycles. The simultaneous large number of critical patients exceeded the capacity of the personnel to provide adequate care, and this caused potential complications related to the stress of healthcare workers.^{1,2}

Heterotopic ossification (HO) consists in the formation of bone tissue in areas of extraskelatal soft tissue where there is usually no bone.³

There are two typical presentations of HO: hereditary and acquired. The latter is more prevalent and is primarily observed in patients with prolonged immobilization following musculoskeletal traumatic injuries, neurological injuries, major burns, ARDS, or major surgeries.⁴

Prolonged immobilization is a common factor among patients with traumatic brain injury, spinal

cord injury, ARDS from other causes, and severe COVID-19.⁵

Tissue injury results in the invasion of inflammatory cells, causing an alteration in cells with mesenchymal origin. This impairment can lead to an osteogenic or osteochondrogenic program as mesenchymal cells differentiate into osteoblasts.⁶ The systemic inflammation, altered calcium metabolism, and local myositis seen in patients with COVID-19 could potentially trigger this effect.⁷

Recently, HO has been reported as a complication associated with severe COVID-19 patients who underwent extended periods of MVA and prolonged hospital stay.⁷ In the vast majority of cases, heterotopic ossification was identified after hospital discharge, with pain, limited range of motion, and joint stiffness as the symptoms that triggered suspicion. Subsequently, the diagnosis was confirmed through imaging studies.^{5,8,9}

CASE REPORT 1

A 43-year-old male patient was admitted to the ICU for severe COVID-19 pneumonia, after two days of hospitalization in a general ward, where hypoxemia persisted despite receiving high concentrations of oxygen. The only comorbidity presented by the patient was Class I obesity. Upon admission to the ICU, the patient required MVA and met the criteria for severe ARDS.

During the initial 10 days in the ICU, the patient underwent four alternating prolonged prone po-

sitioning cycles, totaling 192 hours in that period and in that position. Until day 23 in the ICU, the patient received deep sedation and neuromuscular blocking agents. Complications included infectious events, a sacral pressure ulcer, and intensive care unit-acquired weakness (ICUAW). After discontinuing neuromuscular blockade and maintaining a superficial level of sedation, the patient's muscle strength, assessed using the MRC scale, scored 38/60. This score fell below the cutoff point of 48/60. [10]. The patient was weaned from MVA on day 31 of ICU stay, and was discharged from the hospital on day 52 since admission, without requiring supplementary oxygen and with a MRC score of 50/60. Throughout the hospital stay, the individual had an average daily intake of 1044 mg of calcium, 728.6 mg of phosphorus, and 737.6 IU of vitamin D. The average daily intake of corticosteroids was 9.29 mg (0.093 mg/kg/day) of dexamethasone.

Six months after discharge, the patient presented with pain and limited external rotation movement, and inability to abduct both hips. A pelvic and hip CT scan was requested, revealing bilateral HO of the hip (Fig. 1A and 1B).

CASE REPORT 2

A 58-year-old patient, hypertensive and with Class 1 obesity, hospitalized in a general ward and diagnosed with severe COVID-19 pneumonia suffered an ischemic stroke and was transferred to the ICU. The patient's respiratory condition deteriorated,

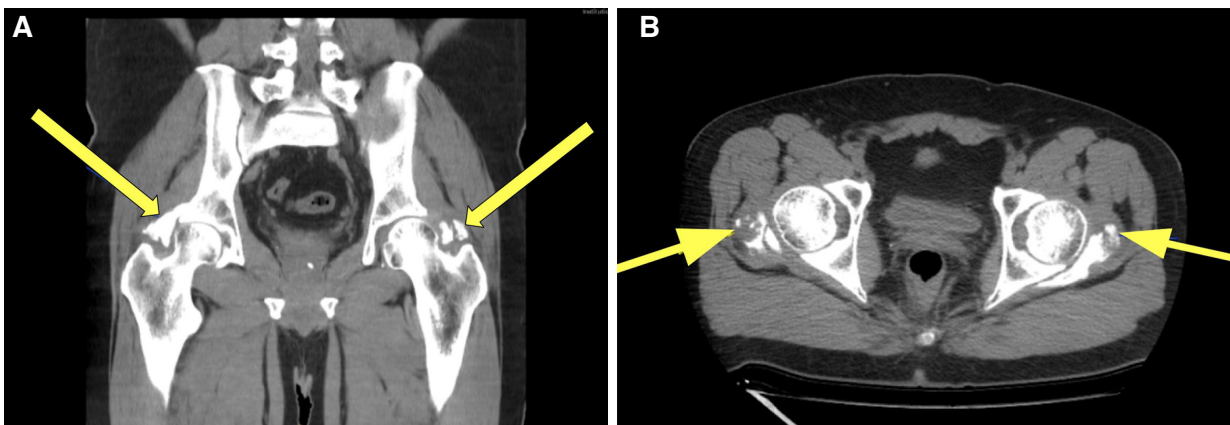


Figure 1. Pelvic and hip CT scan. 1A Coronal plane and 1B Axial plane. In both images, the arrows indicate the presence of heterotopic ossification.

requiring MVA. The patient received two prone positioning cycles, totaling 60 hours within the first 10 days of ICU stay. He/she experienced infectious complications and a sacral pressure ulcer. Weaning from MVA was achieved after 39 days. The patient remained in the ICU for a total of 45 days and was discharged from the hospital 111 days since initial admission. Throughout the hospital stay, he/she had an average daily intake of 2,359.34 mg of calcium, 1,538.6 mg of phosphorus, and 1,190.8 IU of vitamin D. The average daily intake of corticosteroids was 7.75 mg (0.072 mg/kg/day) of dexamethasone. Upon discharge, the patient did not require oxygen therapy but presented with a moderate right brachio-crual motor deficit, ataxia, visual field impairment, and gastrostomy tube feeding due to swallowing disorder. One year post-discharge, there was functional improvement, but with evident limitations in movement unrelated to the motor deficit. A pelvic CT scan was performed, revealing heterotopic ossification in both hips. (Fig 2A and 2B).

As of the current date, there has been no surgical opportunity.

DISCUSSION

The published cases of HO in patients with COVID-19 occurred in the context of severe forms of the disease, involving prolonged hospitalizations and

invasive ventilatory support due to ARDS^{5-9,11-13}. As with any cause of severe ARDS, paralysis and deep sedation were part of the therapeutic approach.^{14,15}

During the stay of the two described patients, the occupancy rate of the ICU exceeded between 66 % and 100% its maximum capacity. That is to say, the occupational rate was 166% and 200 %, and the workload of the nursing staff, measured by TISS-28, was 72 points, nearly double the workload manageable by a nurse [own data]. Infectious complications such as mechanical ventilation-associated pneumonia, catheter-associated infections, and pressure ulcers caused by the decubitus position tripled the average value of the service. In this context, motor kinesiotherapy was postponed due to the need to address urgent circumstances, contributing to prolonged periods of immobilization. The reduced bedside times interfered with the proper implementation of ventilatory weaning protocols, resulting in longer periods of MVA and ICU stay. Consequently, there was greater use of neuromuscular blocking agents and sedatives, generating prolonged patient immobilization.

Some publications addressing the pathogenesis of HO consider immobilization as an associated factor, without specifying the differences between active and passive motion. The work of Stoiria et al, shows a four times higher prevalence in COVID-19 distressed patients compared to those with other causes of ARDS.

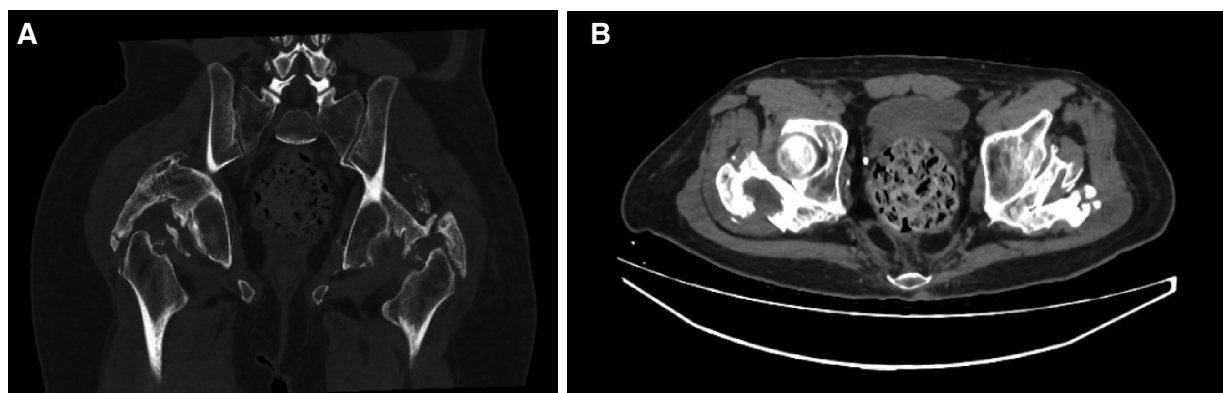


Figure 2. Pelvic and hip CT scan. 2A Coronal plane and 2B Axial plane. In both images, the arrows indicate the presence of heterotopic ossification.

We do not know the dose values of parathyroid hormone, phosphorus, or vitamin D. However, the intake of calcium, vitamin D, and phosphorus were adequate for baseline needs. Regarding the use of corticosteroids, the doses were very high, and were consistent with what was reported by Stoira et al. While some characteristics specific to SARS-CoV-2 infection are suggested, such as humoral alterations, disturbances in calcium metabolism, inflammatory response, and direct muscle injury, the conclusion is that prolonged immobilization is the only relevant factor in the multivariate analysis. The recommendation is early passive motion as a preventive method for the development of HO.⁷

CONCLUSION

Our case report identifies factors that have been mentioned in the literature as possible causes of HO in COVID-19 patients. This includes the prolonged use of sedatives and neuromuscular blockers in patients experiencing intense inflammation. The critical condition and therapeutic strategy result in long periods of immobilization during the ICU stay.

However, the above description does not fully explain the higher prevalence of HO in patients who experienced ARDS due to COVID-19 when compared to patients who suffered ARDS from other causes. Thus, there are no differences regarding the inflammatory processes or the recommendation to use deep analgesedation and neuromuscular blockade.

We interpret that the workload generated by patient care during the pandemic peaks had a significant influence and caused unusual situations in daily practice. This included prioritizing respiratory kinesiotherapy over motor intervention, difficulty in implementing MVA weaning protocols, and less time spent at the patient's bedside due to isolation conditions.

As a result, this could have led to more days of sedatives and neuromuscular blocking agents, prolonged mechanical ventilation, and the delay or impossibility of passive and active motion in patients (all circumstances favoring heterotopic ossification).

We believe that the higher prevalence of HO in severe COVID-19 could serve as a stress marker

of the healthcare system. We think it is relevant to conduct future research to assess this association.

Conflict of interest

Authors have no conflicts of interest to declare.

REFERENCES

1. Shreffler J, Huecker M, Petrey J. The Impact of COVID-19 on Healthcare Worker Wellness: A Scoping Review. *Western Journal of Emergency Medicine*. 2020;21: 1059-66. <https://doi.org/10.5811/westjem.2020.7.48684>
2. Castro HM, Prieto MA, Muñoz AM. [Prevalence of burnout in healthcare workers during the COVID-19 pandemic and associated factors. A cross-sectional study]. *Medicina*. 2022;82:479-86.
3. Sun E, Hanyu-Deutmeyer AA. *Heterotopic Ossification*. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
4. Shehab D, Elgazzar AH, Collier BD. Heterotopic ossification. *J Nucl Med*. 2002;43:346-53.
5. Meyer C, Haustrate M-A, Nisolle JF, Deltombe T. Heterotopic ossification in COVID-19: A series of 4 cases. *Ann Phys Rehabil Med*. 2020;63:565-7. <https://doi.org/10.1016/j.rehab.2020.09.010>
6. Meyers C, Lisiecki J, Miller S, Levin A, Fayad L, Ding C, et al. Heterotopic Ossification: A Comprehensive Review. *JBMR Plus*. 2019;3: e10172. <https://doi.org/10.1002/jbm4.10172>
7. Stoira E, Elzi L, Puligheddu C, Garibaldi R, Voinea C, Chiesa AF, et al. High prevalence of heterotopic ossification in critically ill patients with severe COVID-19. *Clin Microbiol Infect*. 2021;27:1049-50. <https://doi.org/10.1016/j.cmi.2020.12.037>
8. Aziz A, Choudhari R, Alexander AJ, Allam E. Heterotopic ossification post COVID-19: Report of two cases. *Radiol Case Rep*. 2021;16:404-9. <https://doi.org/10.1016/j.radcr.2020.12.002>
9. Vardar S, Özsoy Ünübol T, Ata E, Yılmaz F. A case report of a patient with COVID-19 infection and widespread heterotopic ossification. *Turk j phys med Rehabil*. 2022;68:149-53. <https://doi.org/10.5606/tftrd.2022.8172>
10. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. *Critical Care*. 2015;19:274. <https://doi.org/10.1186/s13054-015-0993-7>

11. Serrano ML, Lima Serrano M, González Méndez MI, Carrasco Cebollero FM, Lima Rodríguez JS. Factores de riesgo asociados al desarrollo de úlceras por presión en unidades de cuidados intensivos de adultos: revisión sistemática. *Med Intensiva*. 2017;41:339-46. <https://doi.org/10.1016/j.medin.2016.09.003>.
12. Van Ochten NA, Shori A, Puderbaugh MA, Benert J, Krishnamurthy M. Heterotopic ossification in COVID-19 patient on anticoagulation with limited treatment options. *Medicine: Case Reports and Study Protocols*. 2022. p. e0212. <https://doi.org/10.1097/MD9.0000000000000212>
13. Brance ML, Cócáro NM, Casalongue AN, Durán A, Brun LR. Extensive progressive heterotopic ossification post-Covid-19 in a man. *Bone*. 2022;155:116287. <https://doi.org/10.1016/j.bone.2021.116287>
14. Chanques G, Constantin J-M, Devlin JW, Ely EW, Fraser GL, Gélinas C, et al. Analgesia and sedation in patients with ARDS. *Intensive Care Med*. 2020;46: 2342-56. <https://doi.org/10.1007/s00134-020-06307-9>
15. Hraiech S, Yoshida T, Annane D, et al. Myorelaxants in ARDS patients. *Intensive Care Med*. 2020;46:2357-72. <https://doi.org/10.1007/s00134-020-06297-8>