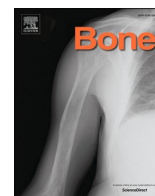




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## Case Report

## Extensive progressive heterotopic ossification post-Covid-19 in a man



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## ABSTRACT

Heterotopic ossification (HO) is the formation of extraskeletal bone in muscle and soft tissues and could be genetic or non-genetic. The classic presentation of non-genetic HO is in young adults with a clear history of local trauma, surgery or prolonged immobilization after spinal cord and traumatic brain injuries. Genetic HO has a significant clinical severity compared to non-genetic causes and includes fibrodysplasia ossificans progressiva (FOP). FOP is an extremely rare genetic skeletal disorder characterized by congenital malformations of the great toes and progressive heterotopic ossification that forms qualitatively normal bone in characteristic extraskeletal sites affecting skeletal muscles, fascia, tendons, and ligaments. Previously, it has been reported an association between SARS-CoV-2 infection (COVID-19) and HO or FOP exacerbation with unclear etiopathogenesis. The possible mechanisms could be prolonged immobilization and systemic inflammation.

Here, we describe the case of a 55-year-old apparently healthy man who suffered from a severe SARS-CoV-2 infection after that he experienced an extensive and progressive heterotopic ossification around the shoulders, the elbows, the hip, the knees, and the ankles.

Because of the clinical severity, the painful soft-tissue swelling, the progressive HO, and the bilateral congenital hallux valgus deformity, a late-onset atypical FOP was suspected. Nevertheless, no variant of clinical significance has been identified in the coding regions and splicing sites in the ACVR1 gene and no deletions and/or duplications have been identified in exonic regions.

## 1. Introduction

Heterotopic ossification (HO) is defined as the formation of extraskeletal bone in muscle and soft tissues. Some HO lesions may be small and clinically irrelevant, while others are associated with high morbidity. It can have a genetic or non-genetic etiology [1].

The classic presentation of non-genetic HO is in young adults with a clear history of local trauma or surgery or prolonged immobilization after spinal cord and traumatic brain injuries [1]. The incidence of HO ranges from 11% to 73.3% in traumatic brain injury and from 10% to 78% in spinal cord injury [2] affecting any large joint, including the hip, knee, elbow, and shoulder. In 2020 and 2021, it has been reported an association between HO and SARS-CoV-2 infection (COVID-19) [3–5]. The etiopathogenesis of HO and its association with COVID-19 is unclear. Prolonged immobilization and systemic inflammation directly or

indirectly might be implicated in the pathogenesis of HO. The cytokine storm associated with COVID-19 includes upregulation of factors that have been previously associated with the formation of HO [6].

Genetic HO has a significant clinical severity compared to non-genetic causes and includes fibrodysplasia ossificans progressiva (FOP), previously known as myositis ossificans progressiva. It is an extremely rare genetic skeletal disorder with an apparent prevalence that varied substantially from 0.65 per million in the United States to 1.4 in Sweden [7,8]. It is caused by heterozygous mutation in the ACVR1/ALK2 gene (OMIM: #135100) encoding Activin A receptor type I/Activin-like kinase 2, a bone morphogenetic protein (BMP) type I receptor [9,10]. It is a severely disabling heritable disorder of connective tissue characterized by congenital malformations of the great toes (hallux valgus, malformed first metatarsal, and/or monophalangism) and progressive HO that forms qualitatively normal bone in

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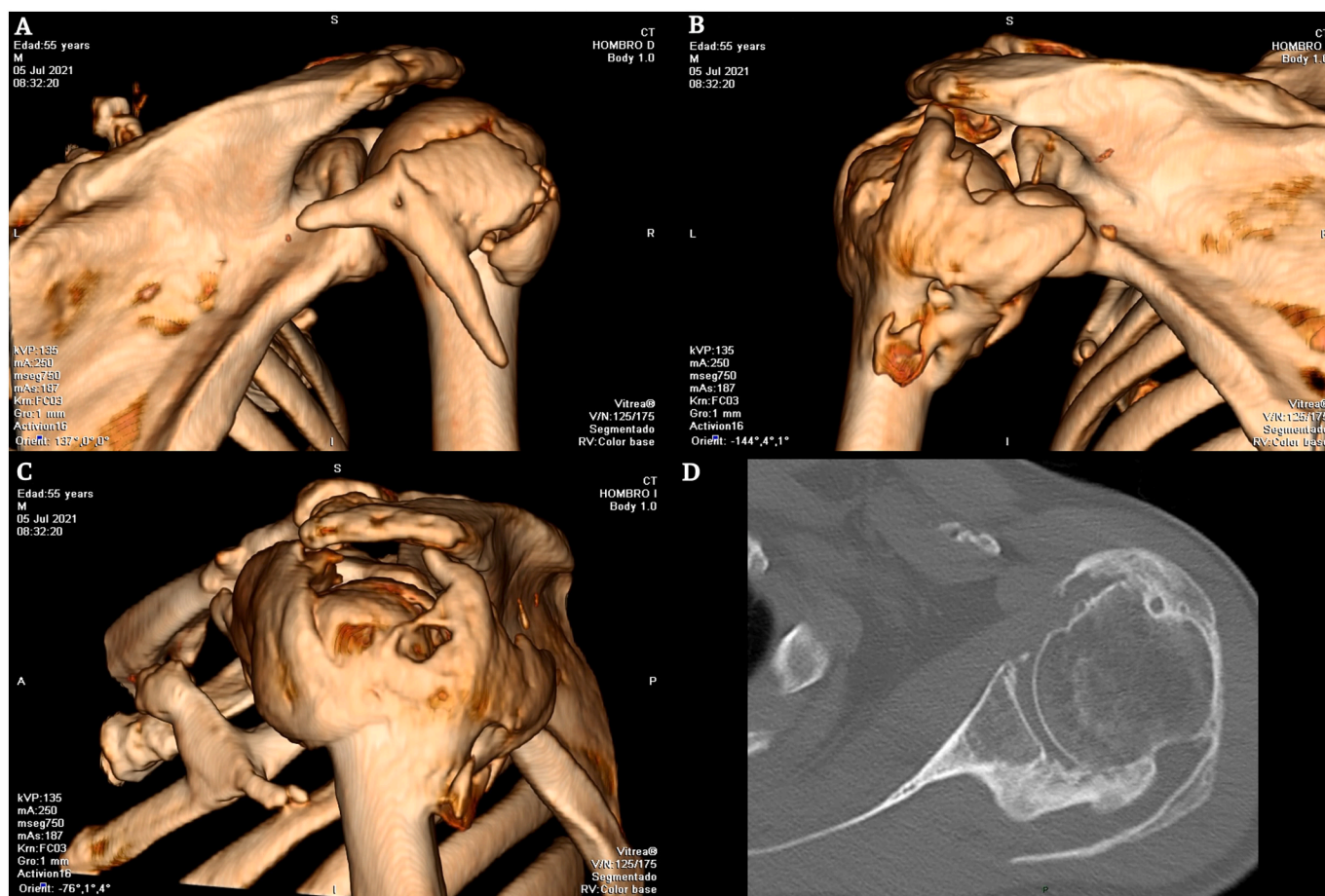
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**Fig. 1.** Computed tomography (CT) of both shoulders (3D reconstruction and axial image). Extensive periosteal mature HO and periarticular mature HO are seen around both shoulders, mainly on the left side. A: On the right humerus there is an irregular-shaped and discontinuous bone spur arising from the posterior aspect of the proximal metaphysis. B, C and D: Irregular shaped bone spurs are seen extending from the posterior, anterior and inferior aspect of the left humerus proximal metaphysis. Also, there is a voluminous and continuous bone bridge between the posterior aspect of the left glena and the humeral epiphysis, with the compromise of the posterior glenohumeral capsule. Another HO is located between the inferior aspect of the clavicular diaphysis and the second costal arc (conforming to a discontinuous osseous bridge).

characteristic extraskeletal sites affecting skeletal muscles, fascia, tendons, and ligaments. Progressive HO throughout the body leads to deformity and loss of motion affecting the normal activities of daily living in FOP patients [11,12]. FOP patients appear normal at birth except for congenital malformations of the great toes. Typically, during the first decade of life, sporadic episodes of painful soft-tissue swellings (flare-ups) occur which has been associated with musculoskeletal trauma such as soft-tissue or neurological injury, intramuscular injections, surgical interventions, among others [1,11,12]. A previous association between FOP flare-ups and influenza-like illnesses was described [13]. In addition, it was described a middle-aged onset FOP in a woman following a brief, seemingly viral, illness [14]. Further, it has been reported a case of FOP exacerbation after COVID-19 infection [15].

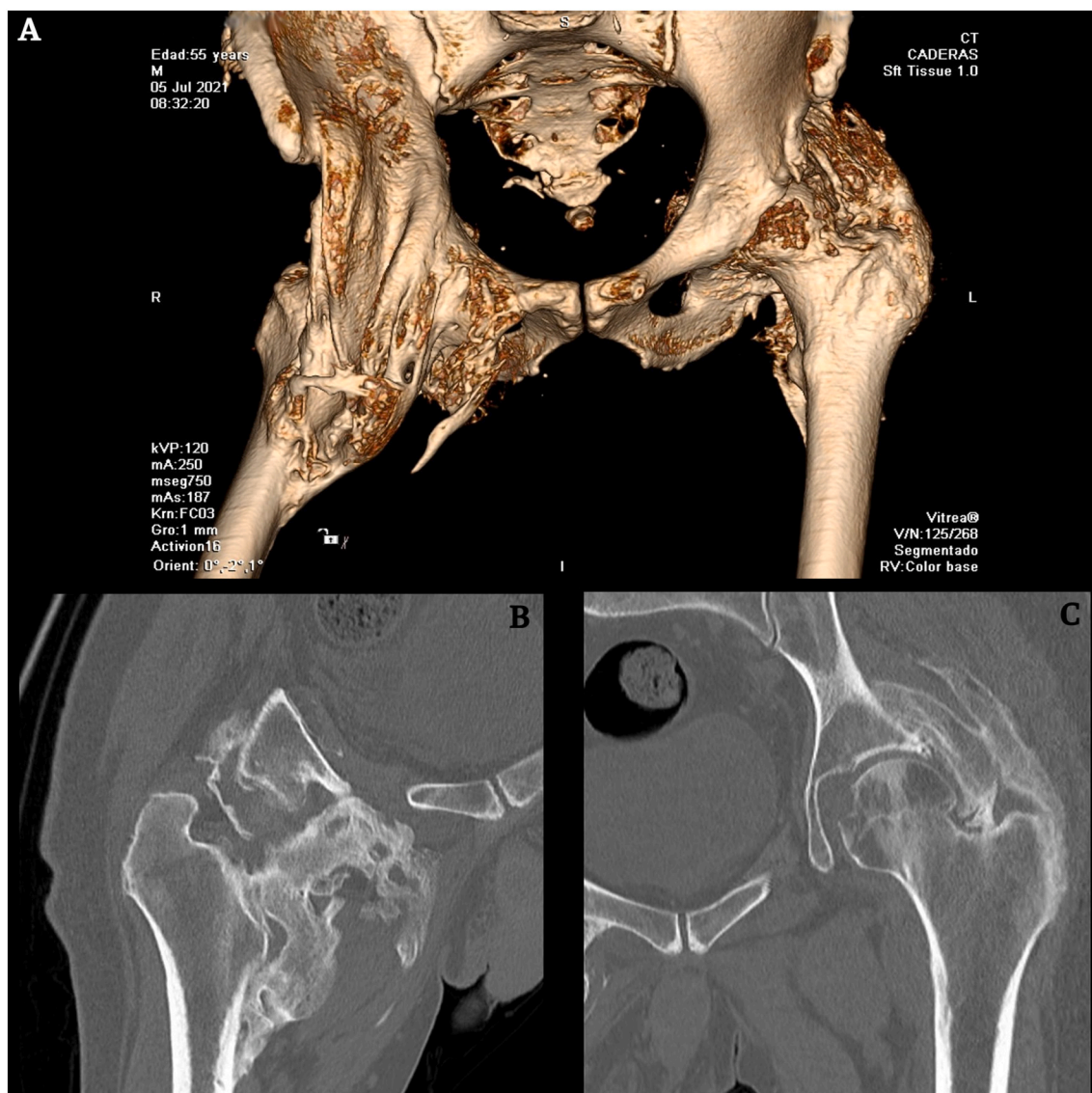
Here, we describe the case of a 55-year-old man apparently healthy who suffered from a severe COVID-19 infection after which he experienced an extensive and progressive HO.

## 2. Clinical case

In September 2020, a 54-year-old man was diagnosed with COVID-19, confirmed by RT-PCR test on a sample obtained from a nasopharyngeal swab for SARS-CoV-2 [16]. Despite he had no risk factors for complications of COVID-19 [17], the patient required hospitalization for longer than 2 months because of COVID-19 pneumonia, supplemental oxygen, and underwent mechanical ventilation. Due to prolonged

intubation, a tracheostomy tube was placed. During the intensive care period, the patient experienced deep vein thrombosis and pulmonary embolism treated with intravenous anticoagulant medication (enoxaparin 40 mg/12 h). After 67 days, he was discharged to a rehabilitation center for polyneuropathy of the critical patient and sacral eschar grade IV because of long-term hospitalization. In addition, he had intense pain (VAS 10/10) and soft-tissue swelling mainly in the hip and left shoulder affecting joint mobility coincident with the first appearance of HO (~9 weeks after SARS-CoV-2 infection). In December 2020, the computed tomography (CT) showed bilateral hip HO located in the right iliac psaos and adductor muscles and left middle and lower gluteal muscles without bones and joint involvement. Synovitis, increased vascularization, and heterotopic calcification were observed in the left elbow by ultrasound (January 2021). Despite physiotherapy, kinesiology, and hydrotherapy treatment, an increase in painful soft-tissue swelling and reduce joint mobility were observed due to HO progression in bilateral shoulder, elbow, hip, knee, and ankle documented by radiography (February 2021).

The patient was referred to our center in June 2021 with intense pain (VAS 7/10), receiving codeine (60 mg/8 h), ibandronate (150 mg/monthly), and oral anticoagulant medication (dabigatran 110 mg/day). A new CT (Activion 16 CT scanner, Toshiba/Canon, Japan) with three-dimensional (3D) shaded was performed. We found an important and progressive HO including irregular bridging and near-bridging characterized by cortical and medullar bone affecting articular joints, muscles,



**Fig. 2.** Computed tomography of pelvis and hips (3D and coronal multiplanar reconstruction). A–B: Massive mature HO along the distal portion of the right iliopsoas muscle (that also involves hip joint capsule and ligaments) down to its insertion at the femoral lesser trochanter and adjacent metaphysis. The HO fuses with the iliac and trochanteric/metaphyseal cortex, conforming to a voluminous and continuous bone bridge. A–C: There is also another voluminous mature HO at the postero-superior aspect of the left hip joint, along with the gluteus minimus and medius muscles (also involves hip joint capsule) down to their insertions at the femoral greater trochanter and adjacent metaphysis (posterior aspect). The HO also fuses with the acetabulum and trochanteric/metaphyseal cortex, conforming to an irregular and continuous bone bridge.

fascia, tendons and ligaments in the shoulders, elbows, hip, knees, and ankles. The most affected sites were bilateral shoulder and hip (Figs. 1 and 2). However, a significant alteration in mobility due to HO was also observed in elbows, knees, and ankles (Fig. 3). In addition, signs of diffuse osteopenia were observed in all skeletal regions examined. Also, a congenital shortening and hallux valgus in the great toes were observed (Fig. 4). Laboratory findings revealed calcemia, phosphatemia, total alkaline phosphatase (111 UI/L, range 40–130), CPK (75 U/L, reference value <190), C-reactive protein, erythrocytation rate, osteocalcin (44.7 ng/mL, range 11–48), and liver enzymes in normal range. An increase in bone alkaline phosphatase (69%, range 20–40) and beta-cross laps (1.66 ng/mL, range 0.2–0.7) were found.

The clinical severity, the painful soft-tissue swelling, the progressive HO affecting skeletal muscles, fascia, tendons, and ligaments with radiographically normal-appearing bone characteristics, and the bilateral congenital hallux valgus deformity, could be indicating a late-onset atypical FOP. Therefore, genetic testing for ACVR1 mutations was

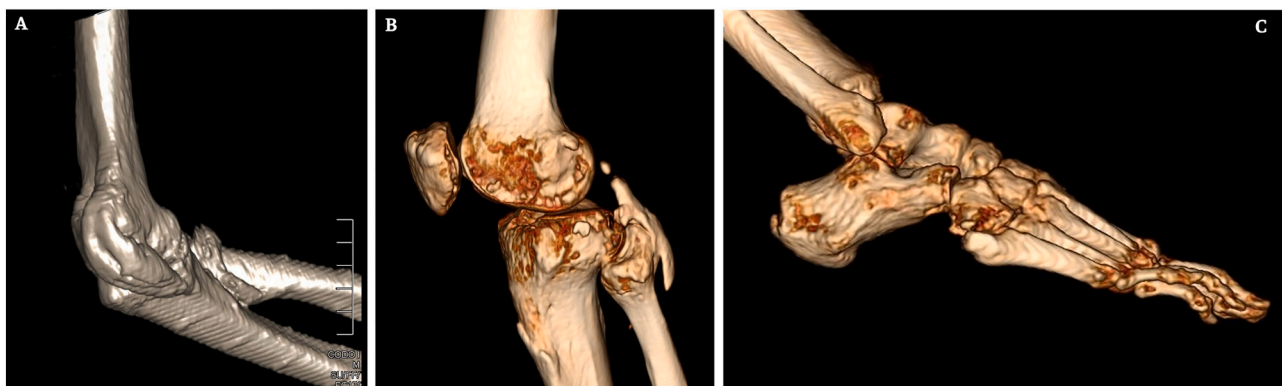
requested in Hérilas (Rosario, Argentina) using next-generation sequencing (NGS) and Genome Analysis Toolkit (Broad Institute, USA). No variant of clinical significance has been identified in the coding regions and splicing sites in the ACVR1 gene. In addition, no deletions and/or duplications have been identified in exonic regions.

In August 2021, the patient had mild pain (VAS 5/10) receiving codeine (60 mg/12 h), ibandronate (150 mg/monthly), and vitamin D (100,000 U/monthly). He is being evaluated by an orthopedic team to determine a surgical strategy.

In summary, we describe a case report of a 55-year-old man who develops sporadic painful soft-tissue swellings and extensive HO after SARS-CoV-2 infection.

### 3. Discussion

The non-genetic HO has been associated with local trauma or surgery or prolonged immobilization after spinal cord and traumatic brain



**Fig. 3.** Computed tomography (3D reconstruction) of the elbow (A), knee (B) and ankle (C). A. There is a mature HO that conforms to a voluminous and continuous bone bridge between the postero-medial aspect of the elbow, between the distal humeral metaphysis and proximal ulna, with the compromise of the subjacent joint capsule. B–C. Mature HO around the knee and ankle, which conforms irregular shaped bone spurs.



**Fig. 4.** Picture of the feet showing the hallux valgus deformity.

injuries [1]. Meyer C et al. reported 4 men (age 39–74 years) with HO (3 around the hip -one bilateral- and 1 around the shoulder) after 30–40 days of severe COVID-19 who required mechanical ventilation [3]. In all cases, a mild increase of serum alkaline phosphatase was described. Aziz A et al. described 2 women (43 and 51 years) with shoulder HO (1 bilateral) after 4 and 5 months after severe COVID-19 who required mechanical ventilation [4]. Serum alkaline phosphatase was increased in one patient and serum creatine kinase was markedly elevated in both cases indicating osteoblastic activity and muscle involvement. Stoira E reported a prevalence of 19.2% (10/52) of HO in patients with severe COVID-19 [5]. Most patients were male (8/10), the median age was 71 years, and the main localization was the hip (7/10). These articles reported HO after COVID-19 were located only in one or two joints. However, the HO in the current case was progressive and clinically more severe affecting muscles, fascia, tendons, and ligaments in multiple regions in the upper and lower limb.

Despite flare-ups of FOP are spontaneous or, most commonly, triggered by soft tissue trauma, a possible association with virus infection. A 3-fold increase of FOP flare-ups during an influenza-like viral illness was

described [13]. However, this data was observed through a questionnaire in 123 FOP patients relying on the memories of patients and their families and influenza-like viral illness was defined symptomatically by having fever or chills, cough, and nasal congestion. Several possible mechanisms have been suggested, including direct invasion of muscle tissue by the virus, activation of proinflammatory transcription factors, and autoimmune processes [13,18]. Grgurevic L et al. described the first report of a 45-year-old female patient with FOP exacerbation approximately 4 weeks post-COVID-19 convalescence [15]. The patient was diagnosed with FOP at the age of four with multiple flare-ups affecting paravertebral muscles, right arm and both knees, masticatory muscle, right femur, infraclavicular region, neck, and right hemithorax and anterior neck until her 44 years of age. Interestingly, this case report is complemented by the patient's plasma cytokine profile analysis before and after COVID-19 infection showing strikingly higher levels of most of the analyzed cytokines (MCP-1, RANTES, IL-1, IL-4, IL-6, IL-8, IL-13, Interferon- $\gamma$ , TNF $\alpha$  and GM-CSF) indicating that COVID-19 might have acted as a trigger for FOP exacerbation.

The current case was an apparently healthy man at the age of 54

years, and except for bilateral congenital malformations of the great toes, he had no FOP manifestations, even after intramuscular injections or musculoskeletal trauma before COVID-19 infection. FOP is an extremely rare genetic skeletal disorder and usually, the first postnatal manifestations begin in childhood [1,11,12]. However, middle-age or late-onset HO has been reported as atypical FOP [12,14,19].

The etiopathogenesis of HO and its association with COVID-19 is unclear. Nevertheless, it is necessary to establish a stronger base of evidence regarding the association. HO was associated with local inflammation, which affects mesenchymal stem cells present in soft tissues [15,20]. In the early stages, there is an intense perivascular lymphocytic infiltration into seemingly normal skeletal muscle followed by the death of skeletal muscle and fibrovascular tissue proliferation [21]. The cytokine storm associated with COVID-19 includes upregulation of factors (IL-6/TNF- $\alpha$  axis) that have been previously associated with HO [6]. We did not find increased level of C-reactive protein and erythrocytation rate, however, they were not measured in the disease activity period. On the other hand, this current patient also has diffuse osteopenia. Many cytokines that are increased due to COVID-19, including IL-1 $\beta$ , IL-6, IL-17, CXCL10, and TNF- $\alpha$  are known to regulate osteoclastogenesis and/or bone resorption suggesting these factors may contribute to the SARS-CoV-2 stimulated bone loss as was suggested using a COVID-19 mouse model (K18-hACE2 transgenic mice) even without changes in body weights, activity scores, and posture scores [22].

In conclusion, HO should be considered in post COVID-19 patients with prolonged immobilization, painful soft-tissue swellings and reduce joint mobility. Preventive physiotherapy including daily joint mobilization as early as possible and anti-inflammatory and pain medications should be taken into consideration. Furthermore, it would be important to consider FOP as a differential diagnosis of HO in the situation of post COVID-19 immobilization to take special precautions and to not exacerbate FOP.

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None.

#### Consent for publication

Written informed consent was obtained to publish his data and images.

#### CRedit authorship contribution statement

MLB was referred the patient and guided the clinical evaluations. NMC delineated the radiological findings. ANC and AD guided the physical rehabilitation. All authors participated in the discussion and clinical case management. MLB and LRB drafted the manuscript. All authors read and approved the submitted manuscript.

#### Declaration of competing interest

María Lorena Brance, Nicolás M. Cócero, Aracelli N. Casalongue, Ariel Durán and Lucas R. Brun declare that they have no conflict of interest.

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