Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Heterotopic ossification in COVID-19: A series of 4 cases

Dear Editor,

Heterotopic ossification (HO) refers to abnormal formation of mature lamellar bone in soft tissues without connection to the periosteum, around proximal articulations, knees and elbows. The hip joint is affected in 77% of cases and the shoulder in 18%, and HO results in muscular and articular pain, joint ankylosis and loss of independence [1]. HO is usually found in patients with central and peripheral nervous system lesions.

We present 4 cases of patients with severe SARS-CoV-2 infection (COVID-19) who required mechanical ventilation and exhibited HO in hips and shoulders.

1. Cases 1, 2 and 3: hip HO

Men aged 64 years old (patient 1), 73 years old (patient 2) and 74 years old (patient 3) presented severe COVID-19 requiring mechanical ventilation and prone positioning for 26, 27 and 30 days, respectively, in an intensive care unit. Comorbidities for patient 1 were high blood pressure, atrial fibrillation and cervical myelopathy. Patients 2 and 3 had a history of high blood pressure and chronic obstructive pulmonary disease. During the intensive care period, patient 2 exhibited deep vein thrombosis of the left superficial femoral and popliteal veins.

After extubation, all patients presented weakness, cognitive disorders and swallowing disorders requiring intensive in-patient rehabilitation. Patients 1 and 2 showed sensory-motor polyneuropathy in the lower limbs that was diagnosed by electroneuromyography. Patient 1 also presented a right brachial plexus lesion most likely caused by compression in the prolonged prone position, which was diagnosed by electroneuromyography. After 39, 40 and 41 days, respectively, all 3 patients complained of acute pain in the groin area associated with a painful limitation of the hip mobility in flexion, extension and rotation that limited gait and sitting. Medical imaging (X-ray, bone scintigraphy and CT) revealed HO.

Patient 1 had bilateral hip HO. For patient 2, CT scan and bone scintigraphy demonstrated left hip HO with peri-articular and intra-muscular ossification in the quadratus femoris, iliopsoas, adductor magnus and external obturator muscles, with signs of osteonecrosis of the femoral head (Fig. 1). For patient 3, CT scan and bone scintigraphy demonstrated left hip HO in the quadriceps femoris and iliopsoas muscles (Figs. 2 and 3). Laboratory findings revealed elevated alkaline phosphatase level, at 200, 126 and 105 UI/L, respectively (normally 38–126).

2. Case 4: shoulder HO

A 39-year-old man presented COVID-19 requiring mechanical ventilation and prone positioning for 28 days in an intensive care

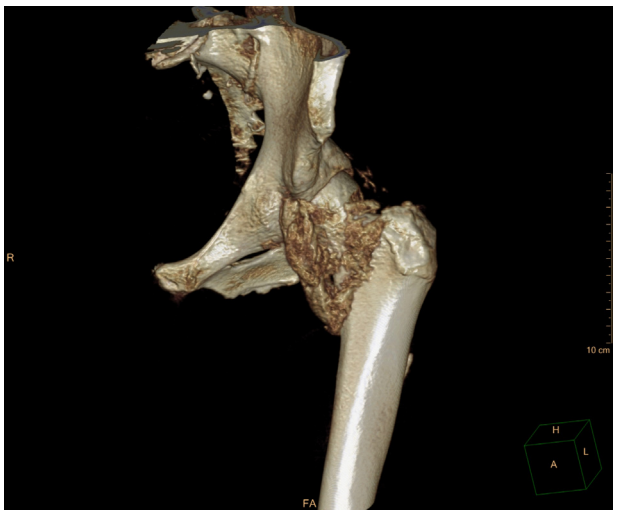

Fig. 1. Patient 2: left hip 3-D CT scan: immature heterotopic ossifications in the left enlarged iliopsoas and obturator externus muscles.

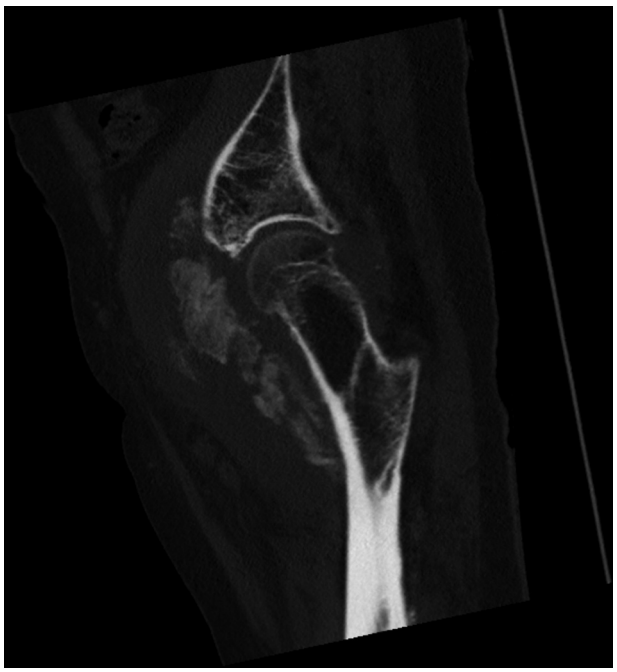

Fig. 2. Patient 3: left hip CT scan: immature heterotopic ossifications in the left iliopsoas muscle.

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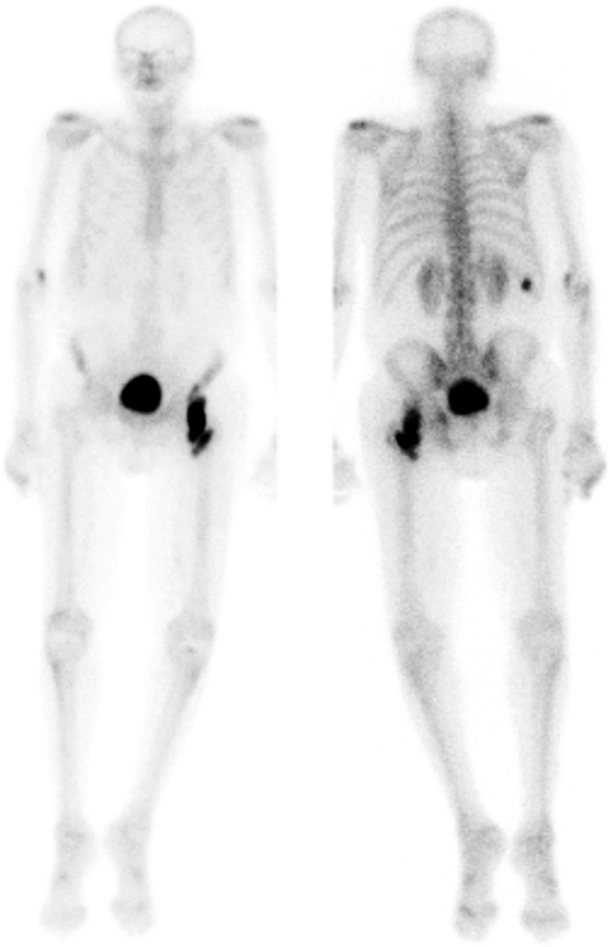

Fig. 3. Patient 3: bone scintigraphy: left hip hyperfixation.

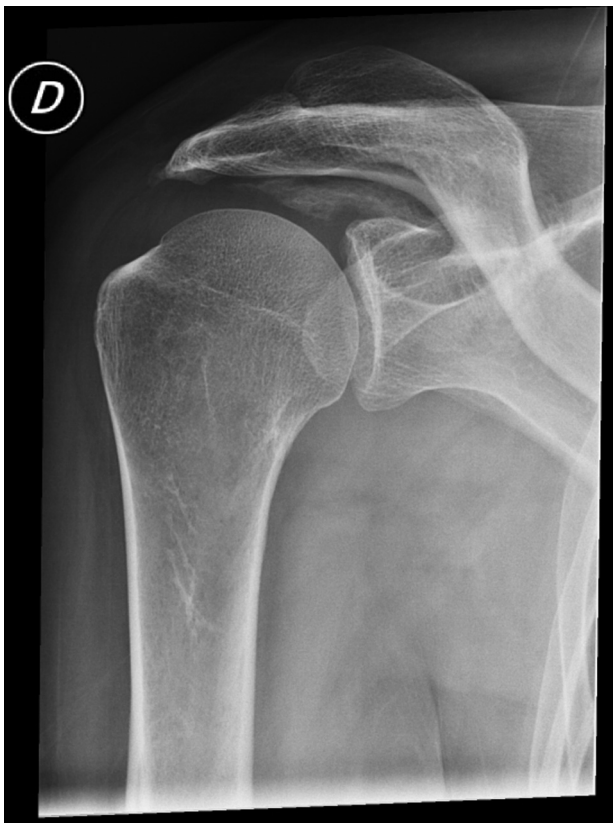

Fig. 4. Patient 4: right shoulder X-ray: mature heterotopic ossifications in the supraspinatus muscle.

unit. The patient had a history of schizophrenia, bipolar disorder and alcohol abuse. He did not show deep vein thrombosis or central or peripheral nervous disorder. At day 30, the patient complained of acute bilateral scapular pain with limited mobility. Medical imaging (X-ray and bone scintigraphy) revealed HO of both shoulders (Fig. 4): alkaline phosphatase level was elevated, at 200 UI/L (38–126).

To our knowledge, these are the first reported cases of COVID-19 complicated by HO. HO usually affects patients with central neurologic system lesions such as traumatic brain injury, stroke, and spinal cord injury [2]. The incidence of HO ranges from 11% to 73% in traumatic brain injury and from 10% to 78% in spinal cord injury and is most likely to occur in the presence of spasticity, extended unconsciousness and bone fractures [3]. Guillain-Barré syndrome, joint replacement surgeries, fractures, muscular contusions, and severe burns are less frequent possible causes [1,4].

HO can cause joint and muscular pain, decreased range of motion, soft-tissue swelling, erythema and heat in the involved region as well as low-grade fever appearing 4 to 12 weeks post-onset [2]. HO exacerbates functional disabilities by increasing difficulty in sitting, eating and dressing [5]. Bone maturation usually occurs after 6 months with histology and radiology findings identical to normal bone [1,5]. In the early stage (2–6 weeks), nuclear bone scans are more sensitive than plain radiography to detect HO, whereas CT allows for better visualization of the heterotopic bone [2]. Laboratory investigation may reveal elevated alkaline phosphatase and creatine phosphokinase levels.

The etiopathogenesis of HO and the association with COVID-19 is unclear [5]. HO is thought to be associated with local inflammation affecting soft-tissue mesenchymal stem cells releasing prostaglandins (particularly prostaglandin E2), which leads to lamellar heterotopic bone formation. Altered acid base homeostasis and tissue hypoxia during the mechanical ventilatory period may play a role in the pathophysiology [6]. In COVID-19, the haematogenous spread seems responsible for the central and peripheral "neuroinvasion" of SARS-CoV-2 [7]. Consequences of this process are neurological diseases such as encephalitis, stroke, critical illness myopathy and neuropathy (CRIMYNE) or Guillain-Barré syndrome. Zeilig et al. reported 6% of patients with Guillain-Barré syndrome affected by HO; blocking the neuromuscular junction enhanced the HO size [8,9]. HO highly depends on inflammation and phagocytic macrophages in soft tissues, but also SARS-CoV-2 infection modulates macrophage-mediated events [5,10]. COVID-19 global inflammation may play a role in HO genesis. That most of our patients had a severe form of COVID-19 reinforces this hypothesis. Another common factor among COVID-19, traumatic brain injury and spinal cord injury (known to cause HO) is prolonged immobilization.

Treatment of HO is challenging. Non-steroidal anti-inflammatory drugs and bisphosphonates are proposed as prophylactic treatment. Early and continuous mobilization is mandatory, and surgical excision is recommended when joint limitation affects autonomy and quality of life (3). Surgical excision should be performed as soon as comorbid factors are under control and HO is sufficiently constituted for excision [11,12]. Early rehabilitation is essential in managing HO and COVID-19 [7]. In the acute phase, COVID-19 patients may present respiratory deficit, cognitive

disorders, central and peripheral nervous system disorders, deconditioning, critical illness-related myopathy and neuropathy, joint stiffness and pain [13]. An estimated 53% of SARS-CoV-1 infection survivors have reported joint pain [13]. HO could be underdiagnosed in patients with COVID-19 requiring intensive care.

HO should be considered in COVID-19 patients with prolonged immobilization in the presence of a painful joint. Early management aims at limiting its progression and maximizing function of the affected joint. The diagnosis is based on clinical manifestations and must be confirmed by medical imaging. Further studies of the impact of invasive ventilation, hypoxia and metabolic disorders on the development of HO are required. Considering the potential functional impairments, early diagnosis and management of this entity is a must.

Disclosure of interest

The authors declare that they have no competing interest.

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