



Mono-articular idiopathic heterotopic ossification in a Coronavirus infected patient admitted in the intensive care unit

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Heterotopic ossification (HO) designates a bone tissue formation within an atypical anatomical location and is commonly diagnosed in patients whom have suffered major traumas. The following case report presents a non-traumatic source of HO. A causality is deduced between the HO formation and an important inflammatory reaction originating from a Coronavirus infection. In contrast to other studies not only is the source non traumatic but the HO formation is unilateral. In systemic inflammatory reactions vigilance towards HO should be enhanced especially in patients treated during prolonged periods of time in intensive care units (ICU).

Keywords: Heterotopic ossification; Coronavirus; ventral decubitus; systemic inflammatory reaction.

INTRODUCTION

Heterotopic ossification (HO) is a complex pathological process resulting in a formation of mature bone in periarticular soft tissue (1, 2). It commonly occurs in a context of any type of musculoskeletal trauma, including total hip replacements (THR) and burn wounds, or neurogenic lesions (3). More rarely, it results from a hereditary condition such as Myositis ossificans. Idiopathic cases of HO are much less documented.

Clinical manifestations of HO include predominantly pain, fever, swelling, erythema, and de-

creased joint mobility (3). The latest stage is ankylosis, which can occur in approximately 10% of patients with HO (4). HO can be localised around all articulations, with the most common being the hip. A radiological examination is primordial in order to differentiate an HO from any malignant bone development such as osteosarcomas or osteochondromas. HO is applied to bone formation at any extra-osseous site (1), without necessarily being in contact with adjacent anatomical bone. In contrast to osteosarcomas, which are almost systematically located within muscle tissue, HO is more commonly located within the connective tissue planes and not constantly within muscle tissue (4).

HO is always a non-articular and extracapsular rapid bone formation typically detected through conventional radiographs as a circumferential ossification with a lucent centre (3). CT scans can be used to further identify the extension of the HO and

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the aspect of the surrounding soft tissue as well as the exact localisation of the bone deposition. Bone scintigraphy is the most relevant imaging technique able to detect early stages of HO due to its high specificity for active cells, bone formation being at its peak during the earlier stage of HO.

Recommended treatment for HO includes a nonsteroidal anti-inflammatory drug (such as indomethacin), a diphosphonate (such as ethane-1-hydroxy-1,1-diphosphate), or local radiation therapy (RT) (to inhibit local soft tissue metaplasia into osteoid matrix) (3) before any surgical treatment is to be undertaken. Passive physiotherapy may be recommended only after the acute phase of HO formation, started at a too early stage may stimulate the inflammation and therefore accelerate HO.

Cases of idiopathic HO formation in intensive care unit (ICU) patients are extremely rare and are commonly associated with more than a single joint region and the condition is often bilateral (3). THR being one of the exceptional unilateral causes which can be explained by its non-systemic origin. Available literature provides only one reported case of elbow and knee periarticular HO formation. We report a case of unilateral hip periarticular HO after ICU stay.

CASE REPORT

A male patient of 74 years of age was admitted to the ICU for a Coronavirus induced severe acute respiratory syndrome. His medical history included hypertension (treated by Amlor 5g 1x/day) and untreated chronic obstructive pulmonary disease (COPD), and an umbilical hernia surgery.

Two weeks after returning from holiday in Egypt, the patient presented a dry cough treated by Amoxicillin and Clavulanic acid, prescribed by his general practitioner (GP). After three days of treatment the patient's condition did not improve and additional symptoms of diarrhoea and fatigue added up. The antibiotic therapy was therefore switched by his GP to Azithromycine. Without further improvement within the following days the patient was admitted to the emergency department where a thoracic scanner and coronavirus nasopharyngeal PCR test were performed. Results were in favour of a Coronavirus infection with bilateral pulmonary

emphysema, pulmonary infiltrations and condensations, concluding the coronavirus induced pneumonitis.

On admission, the patient presented stable parameters with the exception of a severe hypoxemia noted at 91% saturation of oxygen, while under an oxygen therapy of 4 litres through a nasal cannula. This criterion mediated the patient's admission to ICU, an oro-tracheal intubation and a ventral decubitus position for a 27 day duration. His laboratory examination on admission showed an elevated white blood cell count ($12000/\text{mm}^3$) with an increased neutrophil proportion ($10000/\text{mm}^3$), without signs of thyroid disturbance or bone stimulation. A bronchial aspiration did not conclude any bacterial contamination but the presence of *Candida parapsilosis*.

During his stay in the ICU the patient was treated by Plaquenil and Tamiflu for 4 days, and Ceftriaxone for 5 days. On the 11th day a deep vein thrombosis (DVT) was diagnosed throughout the length of the superficial femoral vein and popliteal vein in the left leg. An antithrombotic treatment by Innohep 80 was initiated. After two weeks an elevated C-reactive protein within a blood examination correlated with a positive lung expectoration for *Pseudomonas aeruginosa* which indicated a new antibiotic therapy by Tazocin then Ceftazidim.

The patient was extubated 27 days after his admission and began a rehabilitation process. During passive and active mobilisation with physiotherapists, stiffness in the left hip was recorded 10 days after extubation. Radiological examination revealed diffuse para-articular ossification located around the left hip (Fig. 1). The patient had no record of coxarthrosis or bone diseases in the past. A CT-scan further confirmed this heterotopic ossification essentially on the anterior aspect of the left hip joint, within the anterior muscular tissues and for the majority, not adjacent to anatomical bone (Fig. 2 and 3). A region of osteonecrosis could equally be seen on the supero-posterior region of the femoral head. The right hip joint showed no signs of ossifications. No other articulations presented symptoms of stiffness. No biological signs of bone disturbance were detected. Following orthopaedic advice, initial management included



Figure 1. — Pelvic radiography revealing immature periarticular ossifications around the left hip.

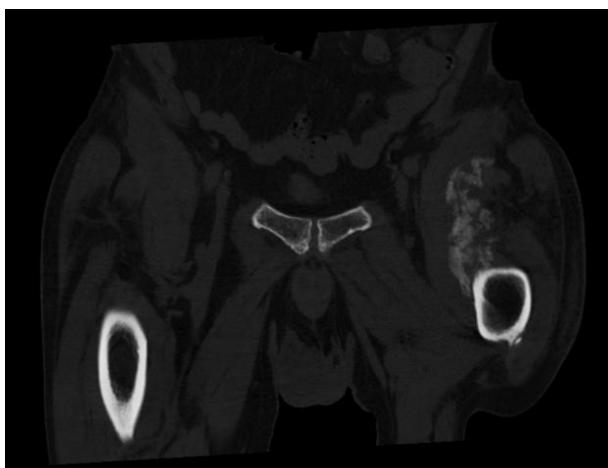


Figure 2. — CT scan of the pelvis and hips in coronal view showing the heterotopic ossification in the soft tissue anterior to the left proximal femur (intramuscular within the Quadratus Femoris muscle, Adductor Magnus muscle, Ilio-psoas muscle and the External Obturator muscle).

physiotherapy and nonsteroidal anti-inflammatory drugs (NSAIDs). Although initial concerns had been made, in late April, the World Health Organisation (WHO) took the position that NSAIDs do not increase the risk of adverse events or affect acute healthcare utilization, long-term survival, or quality of life, in a coronavirus infected patient (5). It was also concluded that the patient was no longer at an acute phase of the COVID-19 infection when the treatment for HO was initially started and therefore less at risk of developing adverse effects of NSAIDs.

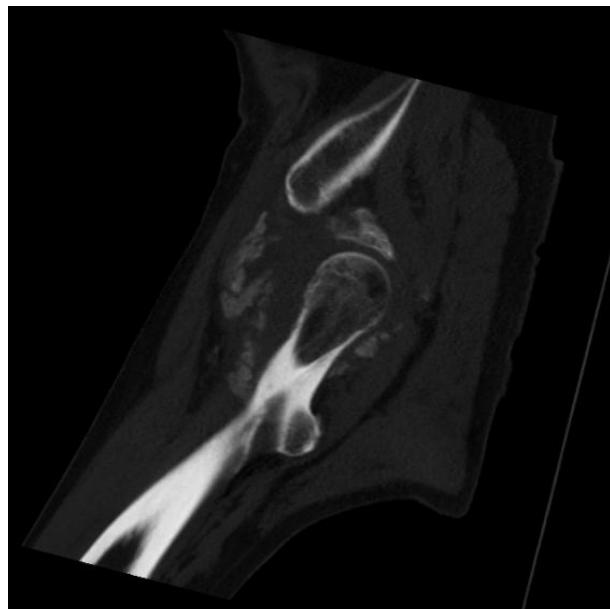


Figure 3. — CT scan of the left hip in sagittal view clearly indicating the large heterotopic ossification anterior to the proximal femur and a very small amount lodged posteriorly.

Although the patient showed small positive signs of regression of HO such as progressive increased mobility of the hip, the final stages of treatment were pursued in another institution due to the patient's geographic preference. No final result can therefore be reported regarding the efficiency of the treatment option in the present case.

DISCUSSION

The bone that forms with the development of HO is composed of both cancellous and lamellar bone tissue (4) not simply calcifications. The exact physiopathology behind this bone formation is yet to be clearly acknowledged. Numerous studies show that various agents released in different situations stimulate the metaplastic change converting mesenchymal cells into osteoblastic cells. The predominant agents include: Bone Morphogenic Protein (BMP), leukotrienes and type 2 prostaglandines (PGE2). The most common situations recorded to release these agents are traumas, primarily polytraumas of high intensity; car accidents, spinal cord injuries, severe burn wounds.

One study screened patients with past histories of ICU stay with HO formation, and all of the recorded cases had classic causes of trauma; no idiopathic cases were described (5). Idiopathic causes are very rarely evoked but can be triggered by the release of bone stimulating agents in situations such as immobilisation, inflammation, venous stasis, and connective tissue disorders (4).

Our patient has no past records of recent trauma. The only recent possible causes of HO formation rest solemnly on the diagnosed Coronavirus infection requiring a four week immobilisation, including a 17 day of ventral decubitus during his stay in the ICU. The coronavirus infection is capable of producing an excessive immune reaction in the host. Labelled as a 'cytokine storm' for its excessive release of numerous agents, the protagonist being IL-6, which may result in extensive tissue damage with dysfunctional coagulation (7). In turn, this immune activation is the primary source altering all three principals of Virchow's triad; endothelial dysfunction, blood flow abnormalities, and hypercoagulability. Resulting in the nomination of COVID-19 as a prothrombotic disease (8).

In literature no similar cases of isolated idiopathic articular locations of HO are recorded. Yet similar settings with HO development in patients in ICU stays and systemic inflammation in post-traumatic patients are more frequent (1). Early stages of fracture repair and osteoblastogenesis are stimulated by inflammation (2). It can therefore be deduced that inflammation from systemic origins can replicate trauma-induced inflammation and equally stimulate fracture repair mechanisms even in ectopic locations. Covid-19 causes massive inflammation boosting cytokines, which increase the liver's production of clotting factors (9). Exacerbated liver activity leads to increased fibrinogen levels and therefore hypercoagulability. In a study conducted by Roumen-Klapp and co. it was concluded that inflammation is a result of the thrombotic process rather than a cause of DVT (10). Although DVTs can be triggering factors for HO formation, the clinical evidence in this case deduces its secondary contribution to the HO formation rather than it being the initial cause of HO.

The HO in this case was located in the anterior aspect of the left hip joint; we therefore suspected a correlation between HO formation and ventral decubitus positioning. No literature records of positioning being a cause of HO are available and a large cohort of patients would be needed in order to compare patient position and HO localisation. It is therefore not possible to pronounce a clear cause and effect of tissue pressure and HO formation. It is to be noted that our patient did not suffer from any pressure ulcers. Therefore capillary-filling pressure (30-32 mmHg) was not exceeded even after having endured prolonged immobilisation. Sufficient precaution was put in place by a pneumatic ripple bed and daily passive mobilisation. Pressure would therefore have to be quantified in order to know the necessary pressure to produce any adverse soft tissue complications that could be a factor leading to HO formation.

CONCLUSION

The present case shows that a systemic inflammation caused by a Coronavirus infection may suffice for HO development. This enhances the practical importance of awareness concerning HO in patients presenting systemic inflammation regardless the absence of common etiologies. In all situations liable to develop large inflammatory reactions such as Covid-19, precautions must be put into place to limit HO formation. Further research could lead to the discussion of the efficacy of combined RT and NSAID therapy as has been advised in the prevention of HO post total hip arthroplasty (THA) (10).

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