

# *Heterotopic ossification following acute illness: a case report*

Researcher (reporters):

Dr Litelu TI: MB., ChB.

Registrar, Department of Internal Medicine, Universitas Hospital and University of the Free State School of Medicine, Bloemfontein, South Africa.

Supervisor: Dr Jansen Van Rensburg BJ, MB., ChB. MMed (Internal medicine), FCP(SA), Cert. Rheumatology

## ***Abstract.***

*Background. Heterotopic ossification is a rare condition typified by formation of bone in extra articular soft tissue. The condition has been linked to several risk factors giving rise to its classification.*

*We report on a case of a 44 year old male patient who was diagnosed with heterotopic ossification following admission for pulmonary TB. The patient does not have the typical risk factors described in recent English language literature. His case is also uncommon due to the diffuse involvement of his joints.*

Case history:

A 44 year old male was referred to us from a neighbouring country (Lesotho) due to stiffness of his elbows, knees and hips after recovering from pulmonary TB in hospital. He was admitted to a hospital in Lesotho in May 2013 and was discharged 3 months later. It was noticed that he was unable to move his hips, knees and elbows at discharge. X-rays revealed fusion of the involved joints due to periarticular soft tissue ossification. He was also diagnosed with HIV-1 infection during admission in Lesotho. The patient had no other known medical conditions. The patient

reported having been confused for part of the admission. Unfortunately no cerebrospinal fluid investigations were done during the admission in Lesotho and on presentation to us, the patient was completely lucid and in control of his faculties.

He experienced no pain in the ossified joints, except when movement was forced. There was no history of trauma to the joints nor to any part of his body leading up to the initial admission. He denied morning stiffness in the uninvolved joints. He also denied fever since discharge from the hospital in Lesotho.

The patient is employed as a supervisor in the military. He does not use alcohol and does not smoke tobacco. There is no family history of skeletal disease and his parents and siblings were all healthy.

Clinical examination revealed a stable patient, wheelchair bound with restricted joint movement in multiple joints. The range of movement was restricted in multiple joints, as follows:

Hips: Right- 0 cm and left- 5 cm in all planes

Knees: Right, flexion and extension- 5 cm and left- 5 cm

Elbows: Right, flexion and extension- 0 cm and left- 5 cm

Ankle (subtalar): Both minimal terminal restriction

All the other joints had normal ranges of motion including the spine.

X-rays done at his initial consultation are shown (figures 1 to 4). No ossification of his wrists was noted on X-ray. He did not have limited movement in these joints.

A skeletal scintigram done during surgical planning revealed increased uptake in multiple areas, including but not exclusive to the clinically and radiologically involved joints. It also revealed decreased uptake in both knees, which had ossification on X-rays. These findings were noted in 2016 and a repeat scan in 2017 showed a similar pattern, despite the patient's condition being present for over five years in 2017.

A CT scan of the right hip reported osteoarthritis of the right hip apart from the ectopic bone mass.

Some of his blood results are shown in table 1. His HIV infection was well controlled on a

primary regime of anti-retroviral therapy prescribed in Lesotho. Consisting of a once a day combination of Tenofovir, Lamivudine and Efavirenz. He was diagnosed with vitamin D deficiency and a secondary hyperparathyroidism, which may contribute to an abnormal calcium to phosphate ratio.

He was discharged from our unit on his anti-retroviral therapy, vitamin D and calcium supplementation.

The patient was handed over to our centre's orthopaedic department to continue with surgical therapy. He had his first surgery in August 2017. The right proximal femur was operated on with good results. He has done well in rehabilitation of this joint. The surgical team chose total hip replacement rather than resection of the heterotopic bone due to extensive osteoarthritis of the joint. He is scheduled to undergo further surgery as planned by the orthopaedic department.

## Literature review

### *Introduction.*

Heterotopic ossification (HO) is a condition characterised by formation of mature lamellar bone outside of the periosteal borders of the skeleton.<sup>1,2,3</sup> Other calcium deposition bodies, outside of the skeleton, are differentiated from it by not being lamellar nor mature bone. These other extra-skeletal conditions include processes such as malignant calcification, calcinosis cutis and dysmorphic calcifications. The pathogenesis and radiologic images of these other conditions differ in comparison to HO. Heterotopic

ossification is the umbrella term for three groups of conditions. These are classified as follows:

- Congenital myositis ossificans
- Post traumatic/ non congenital myositis ossificans
- Neurogenic heterotopic ossification.<sup>3,4</sup>

Some authors use different subtype classifications with all or two of these conditions grouped into a class.<sup>2</sup> However in some literature this condition is seen classed under the larger umbrella syndrome of Ectopic calcification as a general term to also include the other conditions already mentioned above.<sup>5</sup> This discussion will focus on the third group of conditions. This group is often referred to as heterotopic ossification in the literature.

Figure 1



Figure 2



Figure 3

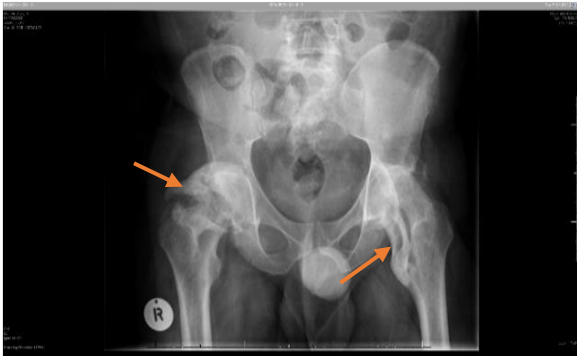


Figure 4



Figures 1 to 4: Pictures of presenting X-rays showing the ossification (orange arrows) of the patient's elbow, knee and hip joints

Figure 5



Figure 6



Figures 5 and 6: X-rays of the patient's pelvis showing total hip replacement of the right hip

	September 2015	2016	2017
Sodium- mmol/l	141	145	139
Potassium- mmol/l	4,7	3,9	5,0
Urea- mmol/l	3,6	4,0	4,4
Creatinine- $\mu$ mol/l	76	92	64
Calcium- mmol/l	2,38	2,31	2,39
Phosphate- mmol/l	1,02	0,85	
Parathyroid hormone- pmol/l	13,6		11,9
Vitamin D nmol/l	42,08	32	12,4
HIV viral load	Less than 150RNA copies		

Table 1: The patient's laboratory results over time

Figure 7

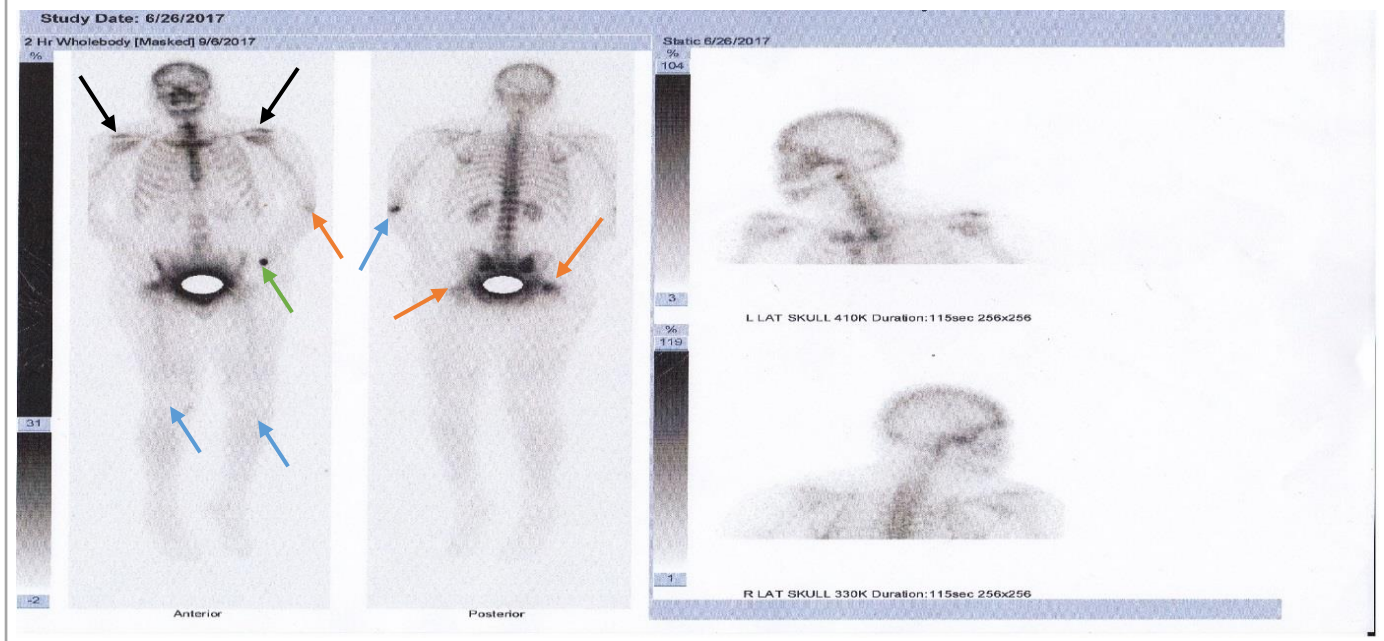


Figure 7: Skeletal scintigram showing high activity in the involved joints (orange arrows) while others show little uptake (blue arrows). The left wrist shows high activity (green arrow), a result of extravasation of tracer around the access point. Some joints show high activity even though they clinically showed no limitation of movement (black arrows)

From henceforth, the term HO will be used to describe the patient's condition and not the whole group.

### ***Aetiopathology.***

No direct cause of HO has been described. Recent evidence suggests a complex event, involving the interaction of bone morphogenetic protein (BMP), the endothelium and the interstitial stem cell differentiation.<sup>6,7,8</sup> There is also evidence to suggest that hypoxia may drive the condition through oxidative stress and chymase expressing mast cells.<sup>9</sup> The endothelium has been shown to play a critical role in the formation of this bone mass, but other factors are also likely involved as the suppression of endothelial growth does not completely stop the occurrence of HO, albeit with evidence from a mouse model.<sup>10,11</sup> The inciting factor however remains elusive. One can only hypothesise from certain common characteristics in the groups of patients who develop the condition.

### ***Risk factors.***

The early cases of HO were noted in children and then later a similar condition was noted in soldiers who had injury to their spinal cords.<sup>4</sup> It has also been noted in patients after total hip arthroplasty.<sup>4,16-18</sup> This has given rise to multiple theories as to the development of this condition. Most theories are directed at the occurrence of HO following local iatrogenic trauma at surgery. Which led to the assessment of different surgical approaches in relation to HO development.<sup>12-15</sup> Studies show that different surgical approaches show different incidences of HO as a complication.<sup>1,15</sup> It has also been shown that by reducing the amount of bone fragments which can

seed in the wound, the incidence of HO following hip arthroplasty is also reduced.<sup>12</sup> This suggests direct seeding as a trigger for HO during hip reaming. This is further supported by the fact that the incidence of HO was reduced by using a plastic draping on the wound during hip arthroplasty.<sup>16</sup> However, the data is conflicting when hip resurfacing, which avoids reaming, is compared to total hip arthroplasty.<sup>14,16</sup> The theory of seeding is limited to patients with local trauma as a possible cause for the development of HO.<sup>17-22</sup> There are also reports of cases of HO following various other episodes of ill health. These include protracted ICU stay, mechanical ventilation, burns and central nervous system (CNS) injury; be it traumatic, infective/inflammatory, a brain tumour or stroke.<sup>17,23-30</sup>

Lane et. al. reported on a patient who developed HO following prolonged immobilisation in ICU.<sup>31</sup> This raises the possibility of immobility as a more important cause of HO, rather than the CNS injury itself. This may be more so in those with neurologic injury, confounding the efforts to try and delineate a causal relationship. This theory is supported by the fact that most patients with neurologic injury causing reduced power in a limb tend to develop HO in the limb with paresis. Pek and colleagues however reported on a patient with stroke who developed HO in the limbs not affected by the paresis that resulted.<sup>30</sup> From recent English language literature it seems likely that the disease is of multi factorial aetiology possibly inciting the proposed pathologic events to result in the bone formation. It may also be speculated that the post traumatic and the non-traumatic HO are two separate conditions with the same outcome. This may explain the difference in the inciting factor in the two groups.

### *Clinical presentation.*

HO can present as a subacute or chronic condition.<sup>11</sup> In the acute phase it may be misdiagnosed as a localised infective process such as an abscess or acute myositis.<sup>32</sup> This is because these patients will often present with features of acute inflammation such as fever, pain, and swelling. Often at this stage the plain X-ray will show no abnormal bone formation.<sup>11,27</sup> A correlation has been demonstrated between the level of the inflammatory response to an injury and the risk of developing HO post-op.<sup>33</sup> The role of inflammation is further strengthened by the effectiveness of NSAIDs as prophylactic agents.<sup>34-39</sup> Whether the inflammatory reaction is an early sign of HO or a risk factor is not clear. Some patients do not have this early disease symptomatology, presenting instead with the more common chronic phase of the disease. This is usually hallmarked by a reduction of the affected joint's range of motion.<sup>9,25,40</sup> There is often no pain at this stage. When present, the pain may range between minimal and tolerable to complete and incapacitating, depending on the grade of disease diagnosed.<sup>4,11,31</sup> There may be localised tenderness due to a fracture after forceful movement of an ankylosed joint. In a proportion of patients, HO is completely asymptomatic.<sup>4,11</sup> The condition may present as an incidental finding on radiographs. Suggesting underreporting of the true prevalence of HO. Even though some series described the prevalence in X-rayed populations, the participants all had conditions necessitating the imaging and thus making this a non-inclusive population.<sup>41</sup> Study of random X-rays might give a better inclusive population to study, more so if these would be a general hospital X-ray cache

rather than an orthopaedic selection. Plain X-rays are also used to grade the disease. The Brooker system is most commonly used. This system grades the disease on severity or proximity of the ossification across a joint. With grade 1 being small islands of bone noted and grade 4 being a completely ankylosed joint.<sup>4,42</sup>

A high index of suspicion is therefore needed to make the diagnosis outside incidental findings on imaging. In a patient who loses range of motion in a joint area following any of the stated risk factors, HO has to form part of the differential diagnoses. A normal X-ray should then not be sufficient to exclude HO, should no other diagnosis be established. It has been proven that MRI is a better imaging modality.<sup>26,30</sup> This is especially true when investigating early disease.<sup>27</sup> The adage of investigating a hypothesis rather than 'investigate and see' approach, remains important as Choi et al, reported on two cases where MRI was used and a wrong diagnosis of myositis and osteomyelitis were made, only to be refuted later when HO became obvious.<sup>32</sup> To summarise, X-rays remain the most commonly used method of investigation. X-rays may however miss early disease, which MRI may elucidate.<sup>27</sup> Bone scintigraphic scanning is reserved mainly for assessing maturity of the ectopic bone in planning for surgery.<sup>18</sup>

## *Treatment*

Surgery remains the definitive therapy. Many patients will not require surgery as the degree of symptoms will be minimal, if at all.<sup>17,18</sup> The aim of surgery is to restore adequate movement of the affected joints, thus obviating the need to operate should there be minimal limitation of joint movement.<sup>25</sup> A better goal will be to improve movement rather than restoring it to normal ranges. This in light of the fact that range of motion in the operated joints is often less than the unaffected joints even after extensive and successful surgery.<sup>40</sup> The bone mass may rarely cause impingement of structures, especially neurovascular bundles. Surgery may have to be undertaken to alleviate this.<sup>26,43</sup>

Medical therapy has mainly been used as prophylaxis in high risk groups and post excision.<sup>11,19,35-38,44-47</sup> The NSAID, Indomethacin is the most widely used medication in this regard. It has been shown to be the best primary prophylaxis. It has also been shown to reduce the incidence of HO when compared to placebo and to reduce the bone mass in those who develop the disease on the medication. NSAID therapy showed no protection in children with severe cerebral palsy and hip abnormalities requiring surgical intervention.<sup>34</sup> One study showed success in resorption of some of the bone mass on indomethacin therapy.<sup>21</sup> There is a paucity of literature on this approach. COX 2 inhibitors are as effective as nonselective COX inhibitors for prophylaxis. They can thus be used to reduce the

gastrointestinal side effects of the nonselective COX inhibitors.<sup>36</sup>

Radiation therapy is used as both primary prophylaxis and secondary prophylaxis.<sup>47</sup> A study found the combination of radiation and NSAID therapy to have some synergy.<sup>19</sup> Radiation was shown to have fewer side effects and to be more effective when compared to NSAID therapy.<sup>47</sup> Though there remains a risk for oncogenesis with radiation therapy. The clinician still carries the responsibility of explaining this to his/her patient when one of these is to be chosen.

Bisphosphonates are effective therapy once HO has developed, while NSAIDs are better as prophylaxis.<sup>38,39</sup> As noted above, surgery remains the mainstay of therapy. It however also carries some risk of complications. Wound sepsis and recurrence of HO are the most prominent of surgical complications.<sup>4,30,40</sup> The recurrence of HO can be treated with surgery and prophylactic measures.<sup>48</sup>

There are some novel therapies still being investigated. Imatinib, a potent PDGF (an important inducer of endothelial growth) inhibitor has been shown to reduce the incidence of HO in mice.<sup>11</sup> Remote ATP hydrolysis has also been shown to prevent heterotopic bone formation.<sup>38</sup>

## *Discussion.*

HO is a rare condition and our patient's case is unique. The patient had no typical risk factors commonly found to be related to the development of HO. Though we do not have a full record of his admission in Lesotho for his index episode of illness, the history does not suggest anything that has been reported to be linked to the occurrence of HO. A possible tenuous link is that of a possible meningitis/encephalitis during the admission. This is postulated due to the patient reporting to have no memory of most of his time in hospital and his relatives relaying that he had been confused. The referring doctor reported that he was admitted for pulmonary TB and was treated for this successfully. As can be seen in the patient's laboratory workup, he had no major biochemical abnormalities at the time of his admission to our facility. This may be because it had already been two years since the onset of joint stiffness and the initial admission.

Though we were not involved in his initial admission we postulate that it is unlikely that the patient was immobilised in all the involved joints. Immobility may be an inciting factor in the development of HO in patients with paralysis. This may explain the cases of HO developing in patients following stroke and trauma with subsequent paralysis. The reported cases of HO following prolonged ICU stay may suggest reduced mobility as a risk factor. A case report of the non-parietic limb being affected by HO may be evidence against this type of theory. The reported patient had injury to the CNS, causing paralysis. HO occurred in limbs not affected by paralysis in this case. The report may lead to theorising that injury to the central nervous system is the main precipitant rather than the resultant paralysis.

Reports of HO following encephalitis may also be evidence of the link between injury to the CNS and developing HO. We postulate that our patient's CNS may have been involved in his initial illness, thus making this the tenuous link to the other reported cases.

HO is now more commonly seen as a complication of hip replacement surgery. Some studies demonstrated a link to the amount of bone fillings that are allowed into the joint space during the procedure as a clear risk factor. A direct link to our patient's case and the other reported cases is not possible. The cases of post-CNS injury and post-operative HO development may be linked by reduced mobility.

Our patient has a dark complexion and we took this as a likely contributor to his vitamin D deficiency. This together with being house bound with little exposure to UV radiation. We also postulate that the vitamin D deficiency is a possible explanation for the delay in the ectopic bone maturation.

Conclusion.

This case presents in a very unusual manner and leaves many questions to be answered. We thus pose questions that we can only postulate answers to at this stage and hope further research can elucidate the answers. The questions which we feel need further probing are:

1. Is there a possible immunologic link to heterotopic ossification? This being that our patient was diagnosed with HIV infection during the initial admission when he developed HO.

2. In comparison to excision, how does joint replacement fare? This being due to the therapeutic option taken by our orthopaedic team as well as it being an established risk factor for this disease process.
  3. Does the vitamin D axis affect the ectopic bone mass the same way it affects normal skeletal tissue?
  4. How would treating the vitamin D deficiency affect the course of the ectopic bone formation, maturation and risk of recurrence post surgery?
- Our patient has a long journey of surgeries and rehabilitation in front of him and we hope to learn from his condition.

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