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Case Report

Acquired Neurogenic Heterotopic Ossification Following Treatment for ADEM: A Case Report and Literature Review

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Abstract
Introduction: *Heterotopic ossification (HO) is the aberrant formation of ectopic bone within the soft tissues, of which the etiology is usually either traumatic or neurogenic. Neurogenic HO is a known but uncommon complication that occurs after a cerebral or spinal insult. The condition may present with a spectrum of symptoms and is often difficult to diagnose clinically.*
Case Report: *We present case study of a 26-year- old man with heterotopic ossification in the bilateral hips that prevented him from walking after being treated for acute disseminated encephalomyelitis (ADEM). He developed severe pain and significantly impaired range of motion of bilateral hips.*
Keywords: *Heterotopic ossification (HO), ADEM (Acute disseminated encephalomyelitis), Hip joint, Knee joint.*

Introduction

Heterotopic ossification (HO) was first described in 1692 by Patin in children with myositis ossificans progressiva. In 1883 and in 1918 a clearer description was provided by Riedel and by De´jerine & Ceillier, respectively. During World War I, HO was predominantly observed in soldiers who had become paraplegic from intra-medullary gunshot wounds.(15)

Heterotopic ossifications (HO) is defined as aberrant formation of ectopic bone containing bone marrow within soft tissues.

There are three possible causes:

1. Progressive myositis ossificans: A rare genetic disease described since 1692 by Patin [1]
2. Traumatic myositis ossificans: The most frequent cause, through direct or surgical trauma
3. Neurogenic heterotopic ossification (HO): described by Dejerine and Ceilier (is usually seen after insults such as spinal cord injury, traumatic brain injury, stroke and cerebral anoxia). (23)

The latter makes the object of this article and occurs in severe medullary and brain traumatisms, less frequently in vascular accidents, encephalitis,

tetanus and severe burns. It is a condition leading to important range of motion limitations, even more so when it localizes near joints. The most frequently affected is the hip joint, then shoulder, elbow and rarely the knee.

Case History

A 26 –year- old man presented to the neurology department with stiffness of the lower limbs, inability to sit with folded hips and legs and impaired movements, which had been gradually worsening since the last three years. The patient gave a history of prolonged immobility and hospitalization due to acute disseminated encephalomyelitis (ADEM).

Imaging

Radiographs of multiple joints were taken.

Bilateral hip joints and the left knee hoint radiographs showed periarticular soft tissue calcifications (Fig 1a & Fig 2). The patient then underwent CT scan of the hip. (Fig 3a&3b)

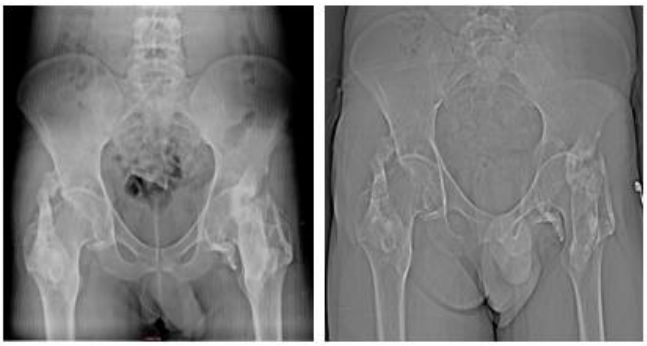

Fig 1. AP Radiograph of the pelvis (1a) and CT scanogram (1b) show extensive periarticular soft tissue ossification around the bilateral hip joints

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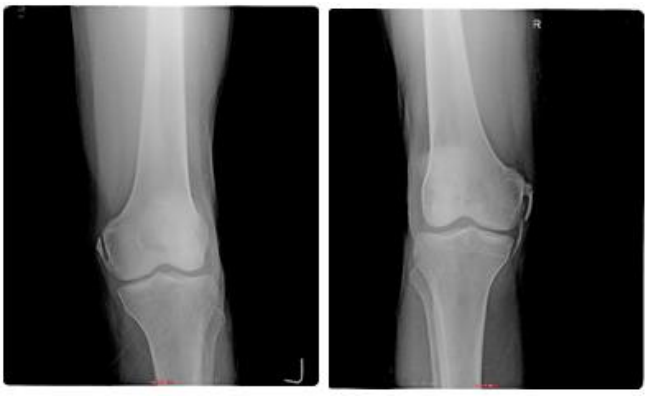

Fig 2. Elongated ossific projections seen in the medial soft tissues of the bilateral knee joints

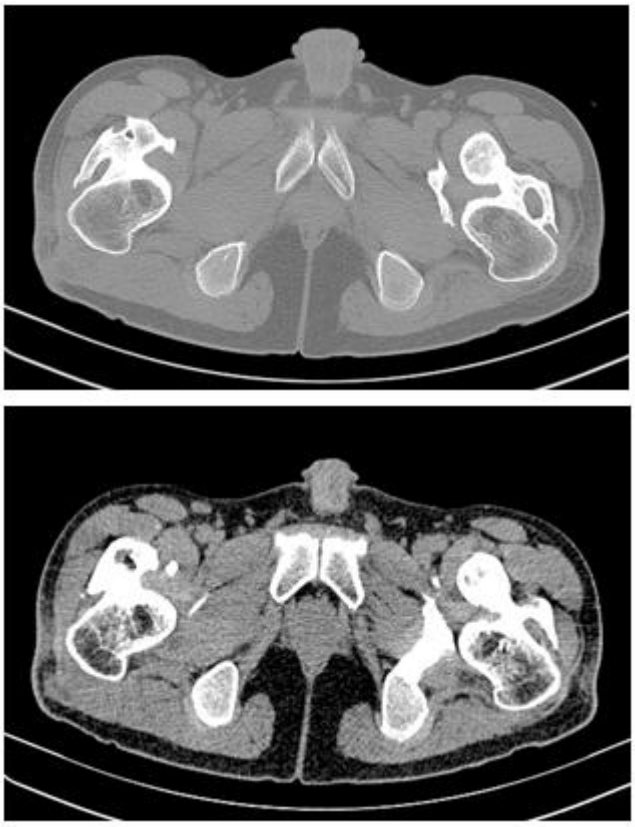

Fig 3. CT Axial sections of pelvis in bone window (3a) and soft tissue window (3b) show multiple bony projections attached to the bilateral proximal femori and from the left ischium

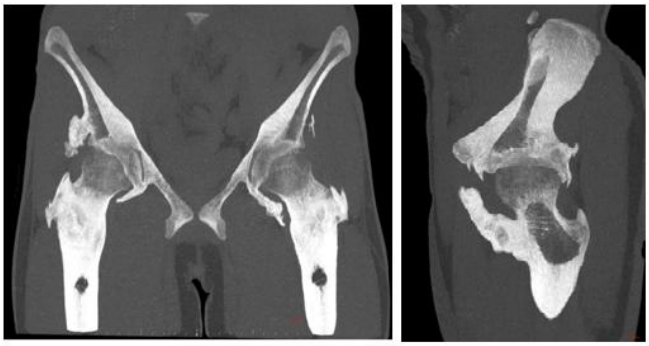

Fig 4. CT Coronal MIP sections of pelvis (4a) CT Sagittal MIP sections (4b) show multiple bony projections attached to the bilateral proximal femori and from the bilateral ischium.

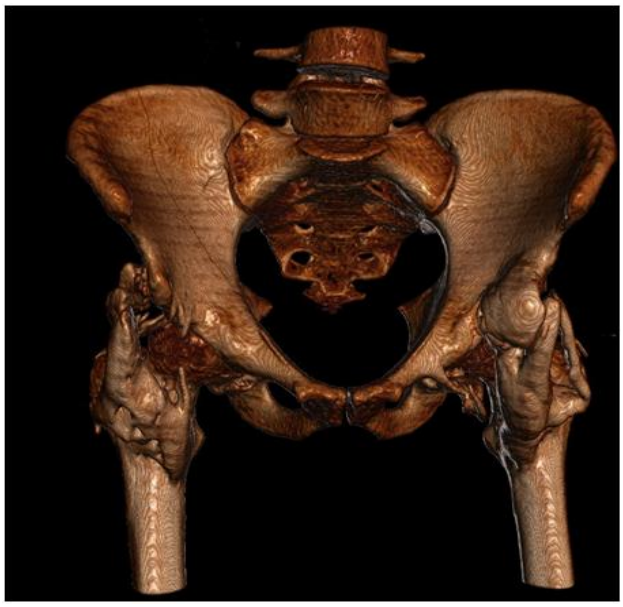

Fig 5. VRT image of the hip with bilateral femori show multiple bony projections attached to the bilateral proximal femori and from the bilateral ischium and bilateral acetabuli.

Discussion

Heterotopic Ossification (HO) is defined as the formation of lamellar bone inside soft-tissue structures where bone normally does not exist [(16).] HO has been described to be mainly post-traumatic and neurogenic in origin.[(3,7)] The incidence of neurogenic HO varies from 11 to 40%[(15)]. In patients with spinal cord-injury the incidence of HO is between 20% and 25%. In closed brain injury HO occurs in 10–20% of patients.[(3)]

Etiology: The etiology of HO is still unknown. HLA-B18 was found to be associated with HO in nerve injuries. However, 75% of patients with neurological injury are HLA-B18 negative [(16)]. Michelsson et al.[(16,17)] stressed the importance of the inducing agent in ectopic bone formation. In an experimental study of osteoarthritis, in which the hind limbs of rabbits were immobilized and daily exercised, they detected ectopic bone formation in the quadriceps. The authors postulated that immobilization and forcible mobilization are the most important triggers of heterotopic bone formation. This combination often underlies the pathogenesis of human HO. These factors are present in patients with paraplegia, severe burns, or severe multiple injuries treated with for example, arthroplasty[(16)]. Shehab et al.[(12)] hypothesised that soft-tissue ossification differs fundamentally from metastatic and dystrophic soft-tissue calcifications. Chalmers et al[(17)] described 3 conditions necessary for HO formation: osteogenic precursor cells, inducing agents and a permissive environment. This would trigger the transformation of mesenchymal cells into bone-forming cells. This transformation is induced by the BMP. Once these conditions are met, mesenchymal cells are recruited, which then proliferate and differentiate into chondrocytes and/or osteoblasts, and ultimately lead to ectopic bone formation[(19)]. Ho SSW[[20]] et al., recently put forward that Prostaglandin E2 is a transmitter to promote the original cell differentiation. Agenetic predisposition may also be implicated in the overall incidence of HO. Particularly in ankylosing spondylitis, hypertrophic osteoarthr-osis and diffuse idiopathic skeletal hyperostosis, bone formation is increased with a higher risk of HO. Other reports have hypothesized that damage to the central nervous system (CNS) results in abnormal activation of factors such as bone morphogenic protein, or systemic factors such as prostaglandin $E_{2..}$ Men are at a higher risk of developing HO than women and also form a larger amount of bone[(16)].

Pathophysiology: Important contributing factors include hypercalcaemia, tissue hypoxia, changes in sympathetic nerve activity, prolonged immobilization, mobilization after prolonged immobilization and disequilibrium between parathyroid hormone and calcitonin[(12)]. The longer the duration of immobilization and the more frequent the periods of exercising, the higher the grade of heterotopic bone formation likely due to microtrauma. Vigorous ranging of joints after 5 weeks of mobilization also resulted in HO but to a much lesser extent.[(5,13,16)]

Histopathology: An important step in the ossification process is fibroblastic metaplasia. Histological studies clearly demonstrated a zone of fibroblastic proliferation, followed by chondroblasts, which eventually transformed into

osteoblasts with blood vessels and Haversian canals. In HO mature lamellar bone is observed peripherally, surrounded by a capsule of compressed muscle fibers and connective tissue. It is suggested that bone forms in connective tissue between the muscle planes and not in the muscle itself. The new bone may be contiguous with the skeleton, but does not involve periosteum. Mature HO shows cancellous bone and mature lamellar bone with blood vessels and bone marrow, with only a small amount of haematopoiesis.[16]

Clinical: patients with HO may present with a spectrum of symptoms, ranging from pain with limitation of ROM to ankylosis of the affected joint.[1] Increased joint stiffness, a limited range of motion, warmth, swelling and erythema are the principal clinical signs of HO. Atypical early HO are hard to distinguish from cellulitis, osteomyelitis, thrombophlebitis and tumor.[12] The rapid development, histologic makeup, and radiographic configuration of distinguish it from other conditions, including osteosarcoma and osteochondroma. Osteomyelitis may represent a more difficult diagnostic challenge.[12]

Diagnosis: Biochemical markers like alkaline phosphatase (ALP) has some certain clinical significance of early diagnosis of HO but has no specificity.[22]

Most sensitive imaging modality for early detection of HO is triphasic bone scintigraphy which can also monitor the metabolic activity and degree of maturity of HO[11]. Specifically, flow studies and blood-pool images will detect incipient HO approximately 2.5 weeks after injury, with findings on delayed scintigrams becoming positive approximately one week later[16]. Activity on the delayed bone scans usually peaks a few months after injury, after which the intensity of activity on these scans progressively lessens, with a return toward normal at 6–12 mo. Most bone scan findings return to baseline within 12 mo. However, in some cases activity remains slightly elevated even though the underlying HO has become mature. During the course of HO, the delayed bone scan may show increased activity even after the flow study and blood-pool images have returned to normal. Serial bone scans have been used successfully to monitor the metabolic activity of HO and determine the appropriate time for surgical resection, if needed, and to predict postoperative recurrence[12] This technique has low specificity, as any local or systemic process that increases bone turnover can result in increased uptake, hence is not recommended for the diagnosis of HO[11]

Current imaging modalities, though helpful in late diagnosis are inadequate to help clinicians detect early HO development. The formation of HO begins within days to weeks of the inciting event. The disease has already spread beyond the point where it can be treated and impeded with oral medications, once visible through these current techniques. That is to say, none of the available prophylactic measures would affect the outcome of HO once the process begun. Therefore, a urgent need exists to improve the current diagnostic modalities for HO which are inadequate to diagnose and intervene on HO at early time-point [21]

Radiological findings

X-ray cannot discover HO until 4–6 weeks[21]

Brooker et al classified post-traumatic HO according to its radiological findings (Table I)[4]

Table I. Classification of HO based on the radiological findings

	Radiological findings
Class I	Islands of bone within the soft tissue around the hip
Class II	Bone spurs from the pelvis or proximal end of the femur, leaving ≥ 1 cm between opposing bone surfaces
Class III	Bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to < 1 cm
Class IV	Apparent bony ankylosis of the hip

Mavrogenis et al further classified neurogenic HO based on the anatomical location of HO: Type I – anterior; Type II – posterior; Type III – anteromedial; and Type IV – circumferential.[7]

Knowledge of the different classifications of HO is important when considering surgical intervention, in relation to operative approach and preoperative planning.

Conventional radiography is commonly utilized at initial evaluation of patients with clinical symptoms suggestive of HO. Typically, a soft tissue mass or swelling is the earliest radiographic finding. Ectopic bone formation can be seen as early as two weeks following surgery. Classically, HO is described as a peripheral zone of calcification with a relatively lucent center, typically by 6–8 weeks post-surgery. The lesion tends to appear smaller and denser in the subsequent four months.[7]

Ultrasonography detects HO sooner than does conventional radiography. Local signs of inflammation in spinal cord injured patients are suggestive of HO. Ultrasonography is the best investigative modality not only for the early identification, but also for the follow-up of HO. It also has high sensitivity and specificity for the early diagnosis of HO 1 week after total hip arthroplasty[16].

On CT, lesion appearances usually parallel those on conventional radiographic images, i.e. bone formation that begins peripherally and ends centrally. As the lesion undergoes further maturation, a zonal pattern of mineralization with the presence of a mature bony cortex is characteristically seen. There is high specificity for HO when such classic zonal appearance is visualized.[8,9] Cross-sectional imaging is useful in the localization of the lesion. However, if CT is done during the earlier stages of maturation, it may show a soft tissue mass with patchy or absent mineralization, which may mimic a soft tissue sarcoma or osteosarcoma (particularly the juxtacortical subtype).[6] Repeat CT after several weeks is useful, as it allows for better characterization upon further maturation and evolution of the lesion.

MR imaging results vary according to the age of the lesion. Early features are nonspecific – heterogeneous high T2-weighted signal is frequently seen within the lesion and a hypointense rim representing calcification may be seen, although this is often indistinct. Intravenous gadolinium administration results in early, intense, heterogeneous enhancement of the lesion, which may be mistaken for osteomyelitis.[6,10,11] After the lesion has undergone several weeks to months of progressive maturation, MR imaging may demonstrate a better-defined hypointense rim corresponding to the mature cortical bone, as well as high T1- and T2-weighted signals developing centrally.[11] Late lesions typically do not enhance, but some may enhance minimally. The appearance of the lesions on MR imaging may mimic radiological findings of atypical lipomatous lesions such as liposarcomas.[10,11].

Treatment: Medical therapy and radiotherapy are available for the treatment and prophylaxis of HO. NSAIDs were recognized as the most effective drugs to prevent the formation of HO after surgery [1]. Most doctors agree that indomethacin is the best choice among NSAIDs not only prevent HO but also slows down the process of HO development. However, the application of NSAIDs is relatively limited, for its adverse drug reaction such as gastrointestinal ulceration, decreased platelet aggregation and renal toxicity [1]. Coventry MB [22] et al. conducted a research with patients who had HO following total hip arthroplasty, and they believed that radiation aids to prevent the formation of ectopic bone. However, the potential side effect that we should consider is carcinogenesis. Despite the risk that it can trigger another round of HO, surgery remains the only treatment option to date once bone tissue has formed. To increase the range of movements of the joints and improve function and quality of life, surgery was a good choice among treatments. Therefore, we choose the method of revision surgical resection in our case study.[2,3,13,14]

Conclusion

HO presents multiple diagnostic and therapeutic challenges. Although clinically significant HO occurs infrequently. Appropriate use of laboratory and imaging data, particularly alkaline phosphatase values, PGE2, and bone scintigraphy, permits early detection and more successful management of this troublesome ailment.

For the diagnosis of mature HO in terms of imaging, the technique of choice is CT, as it

enables better assessment of the osseous nature of the lesion.

The radiologist should be aware of the different aspects of HO at imaging.

Correlation between MR and CT features is critical to accurate diagnosis. When dubious findings are present, CT scan follow-up is advisable. In advanced ossification, imaging is key to correctly time surgical resection.

Clinicians may request CT imaging and/or bone scanning, to confirm the diagnosis of HO, to choose between medical treatment or the appropriate time for surgical resection.

For many patients at risk for HO, either a non-steroidal anti-inflammatory drug (such as indomethacin or EHDP) or local radiation therapy is recommended.

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