Heterotopic ossification: A case series

Donald Hamby, Brian Chau, Mickey Lui, Calvin Fesler, Sarah Humbert, Scott Strum, Brian Kim

ABSTRACT

Introduction: Heterotopic ossification is an underrecognized condition of uncertain etiology encountered by many physicians in the acute setting with pain and fever as common presenting symptoms. When pain and fever occur in the setting of swelling, erythema and/or decreased joint mobility, heterotopic ossification can present like cellulitis, osteomyelitis, thrombophlebitis, and tumor along with many other infectious and rheumatologic phenomena. A high degree of suspicion is required in patients at risk for heterotopic ossification. Although the pathophysiology of this condition is yet to be fully elucidated, certain risk factors have been identified. We present five cases of patients who developed heterotopic ossification secondary to a variety of predisposing conditions: traumatic brain injury (TBI), spinal cord injury (SCI), stroke, and lower limb amputation. Management was a combination of pain control and bisphosphonate therapy in addition to range of motion exercises with skilled therapists.

These cases demonstrate the heterogeneity of conditions that may predispose individuals to the development of heterotopic ossification and highlight the importance of considering such a diagnosis in order to achieve early treatment so as to prevent functional loss and progression that may require more aggressive intervention.

Keywords: Bone, Brain injury, Heterotopic ossification, Spinal cord, Trauma

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INTRODUCTION

Heterotopic ossification is the formation of extra-articular bone in soft tissue adjacent to bone. Heterotopic ossification may be seen in patients with a variety of conditions encountered by clinicians in an acute hospital setting or even in an outpatient setting. Classic risk factors for this type of bone formation include trauma (e.g., long bone fractures) and sequelae of prolonged immobilization from a catastrophic event (e.g., spinal cord injury (SCI), traumatic brain injury (TBI), or stroke). The pathophysiologic mechanism of heterotopic ossification remains to be completely understood, however, science-based theories describe at least three conditions must be met for heterotopic ossification to take place: presence of osteoinductive factors, presence of osteoprogenitor cells,
and an environment conducive to osteogenesis [1–3]. Osteoinductive factors include alkaline phosphatase, transcription factors, bone morphogenetic protein, and various proteases [4–6]. Local inflammatory molecules such as substance P help produce an environment needed for heterotopic ossification formation [6, 7]. It is theorized that mesenchymal stem cells are introduced into soft tissue through trauma and then differentiate into osteoblasts, eventually leading to this unwanted bone formation [7, 8]. We present four confirmed cases of heterotopic ossification in a sub-set population of rehabilitation patients and describe their unique presenting features and clinical course. These cases demonstrate the wide spectrum of patient history profiles that may be encountered in this condition.

**CASE SERIES**

**Case 1: Heterotopic Ossification in Traumatic Brain Injury, and Polytrauma**

A 67-year-old male with a past medical history of hypertension and diabetes mellitus II, presented to our acute rehabilitation facility after a rollover motor vehicle accident two months before. At the time of the accident, he had been ejected from the vehicle, and his Glasgow Coma Scale (GCS) was 6 at arrival to the trauma center. He was found to have an intraparenchymal hematoma of the anterior temporal lobes, right subdural hematoma, and diffuse axonal injury in addition to bilateral rib fractures, bilateral pneumothoraces, and diaphragm rupture with gastric herniation. He was markedly agitated and encephalopathic during the initial hospital stay. He eventually stabilized and was transferred to a long-term acute care facility where he showed slow improvements in mental status. He was later admitted to our acute rehabilitation facility, eight weeks after initial injury.

On admission to acute rehabilitation facility, the patient was confused, intermittently agitated, with a mental status consistent with a Rancho Los Amigos levels of cognitive functioning scale level IV. He required direct nursing supervision for behavioral management and safety. He consistently reported right knee pain throughout his stay, during rest and ambulation with therapy, and did not have history of previous knee injury. On physical examination, he had an immobile enlargement along the medial aspect of the right knee, tenderness to palpation, and full but mildly painful range of motion at the knee. Correlative radiographic imaging showed a 3.5x1.0 cm region of ossification adjacent to the medial femoral condyle (Figure 1). A subsequent three-phase bone scan showed increased focal uptake within the medial right knee corresponding to the osseous fragments - concerning for active heterotopic ossification (Figure 2).

Diclofenac gel 1% 2 g QID PRN was prescribed with direct application to the knee with reported mild relief of knee pain. This was followed by oral bisphosphonate...
therapy with etidronate 20 mg/kg per day. He continued to report right knee discomfort but it was comparatively less than before treatment for heterotopic ossification. Throughout his stay, there was an overall slight improvement of pain and neurological status. However, due to plateau in functional progress, he was discharged to family care shortly thereafter, with plan to continue oral bisphosphonate therapy (etidronate) as an outpatient.

The patient was seen in the clinic three months after discharge from acute rehabilitation, and his neurologic status had notably improved. He was doing well with only mild cognitive impairment and improved ambulation. He and his family reported the knee pain was still present but considerably better, and he had completed the six-week course of the bisphosphonate treatment. Given the excessive geographic burden of commuting to our clinic on a regular basis, he was referred to his primary physician for further management and was discharged from our clinic.

Case 2: Heterotopic Ossification in the Amputee

A 68-year-old male with a history of diabetes mellitus II, hypertension, chronic kidney disease, and chronic right knee pain due to osteoarthritis underwent an elective right total knee replacement. His postoperative course was complicated by recurrent wound and hardware infection that required courses of antibiotics and surgical revisions of the knee replacement. After failing these interventions, he had an above-the-knee amputation on the right.

The patient was admitted to acute rehabilitation facility for amputee rehabilitation and wound care management. His stay was uncomplicated—he met functional goals and was discharged home. Within two months, the patient reported progressive pain at the medial prominence of his residual limb that was interfering with the fit and effective use of a temporary prosthesis. He was eventually referred back to orthopedics and X-ray imaging revealed changes concerning for heterotopic ossification at the distal femoral stump; surgical excision was recommended. Laboratory analysis of alkaline phosphatase remained normal throughout observation and treatment. No perioperative prophylaxis was previously recommended by the surgical team at the time.

Nine months later, the heterotopic ossification was excised and the patient was admitted to acute rehabilitation. The pain at the stump markedly improved with postoperative pain control and progressive range of motion exercises. Having met functional goals, he was discharged home with planned outpatient follow-up with PM&R and orthopedics.

Case 3: Heterotopic Ossification after a Stroke

A 56-year-old male with a history of hypertension and major depressive disorder suffered a right middle cerebral artery (MCA) infarct with resultant left hemiplegia. During or just before the ischemic event, he had a mechanical fall when he was attempting to get out of bed, and landed directly onto his left shoulder. He was initially admitted to an outside hospital and MRA revealed stenosis of the RM1 segment of the right middle cerebral artery.

Upon admission to our acute rehabilitation facility four weeks later, his stroke-related deficits were left hemisensory loss, left hemiplegia (worse in the upper extremity), and mild cognitive impairment. After two weeks, he began complaining of left shoulder pain. Radiographic imaging demonstrated heterotopic ossification at soft tissue of the medial aspect of the proximal humerus.

Etidronate was started immediately after this finding and was continued for six weeks. In addition, outpatient therapy for range of motion and a home exercise program were recommended. At clinic follow-up, he reported to be symptom-free and did not have heterotopic ossification related impairment of his ability to perform activities of daily living (ADLs).

Case 4: Heterotopic Ossification in Traumatic Brain Injury/Spinal Cord Injury

A 55-year-old male without prior medical history was involved in a motorcycle accident traveling at unknown speed while not wearing a helmet. He was intubated at the scene of the accident. On arrival to a local trauma-level emergency department, patient had GCS 3. Focused assessment with sonography for trauma (FAST) scan demonstrated blood in abdomen and pericardium, and he underwent emergent exploratory laparotomy and median sternotomy. He was also found to have several liver lacerations and a right ventricle laceration. Other injuries included a left frontal skull contusion, tentorial subdural and subarachnoid hemorrhage, T7 chance fracture, left scapular fracture, and left greater trochanteric avulsion fracture. He was admitted to our acute rehabilitation facility following an eight-week hospitalization with a severe TBI, ASLA A at T7 SCI, and healing bone fractures. During his rehabilitation, he reported increasing left shoulder pain without history or evidence of trauma to the shoulder acutely. The X-ray was inconclusive for underlying anatomic etiology. However, a triple phase bone scan confirmed presence of heterotopic ossification.

Surgical intervention was not considered for this patient because his shoulder range of motion was not compromised. Etidronate therapy was commenced at 20
mg/kg for two weeks and decreased to 10 mg/kg for 10 weeks at time of discharge. The patient was discharged home without further complication from shoulder heterotopic ossification and with improved pain.

**Case 5: Heterotopic Ossification in Traumatic Brain Injury**

A 17-year-old male without prior medical history was involved in a fall from a pick-up truck resulting in a severe traumatic brain injury resulting in left-sided hemiparesis. Computed tomography scan of head at the acute hospital showed a right frontal, temporal, and parietal subdural hematoma with midline shift. He underwent decompressive craniectomy the same day. Subsequent MRI scan of head revealed additional bilateral basal ganglia infarction. Acute hospital course also included ventriculoperitoneal (VP) shunt placement for hydrocephalus, tracheostomy placement and percutaneous endoscopic gastrostomy tube placement. After these interventions and two months stay, he was transferred to an acute long-term care facility for further management.

After three months stay at an acute long-term care facility, he was transferred to acute rehabilitation to begin inpatient rehabilitation. During his acute rehabilitation stay, the patient reported right elbow stiffness and pain. Additionally, physical therapy noted difficulty with range of motion and pain in the elbows bilaterally. Physical examination noted decreased range of motion, and warmth to the touch. Bilateral elbow X-rays were obtained. Left elbow X-ray showed areas of heterotopic ossification seen posterior to the olecranon fossa, posterior to the humerus, and anterior to the neck of the radius (Figure 3). Right elbow X-ray showed heterotopic ossification adjacent to the medial epicondyle and posterior to the olecranon fossa (Figure 4). He was placed on indomethacin 25 mg three times a day for heterotrophic ossification along with continued physical therapy for range of motion. Over the rest of his hospital course he demonstrated improved pain relief and full participation in therapies. Patient was discharged home with continued indomethacin treatment and physical therapy without complications. Further surgical intervention would be considered for removal of heterotopic ossification after one year when heterotopic ossification would be fully matured.

**DISCUSSION**

These cases demonstrate an array of patients with injuries often seen by both specialists and primary care physicians in acute and outpatient settings. The patients discussed above shared the classic risk factors for heterotopic ossification of prolonged immobilization, an initial traumatic event, and presenting features of pain at the joint involved.

Monitoring for the development of heterotopic
ossification and considering it in the differential diagnosis for patients presenting with new pain at common sites such as hips, knees, or elbows are of utmost importance given possible deleterious effects on pain control, function, and recovery. While radiographs were used frequently in the above cases, they may be negative for 3–6 weeks after symptom onset [9]. Bone scans are considered more sensitive for detecting early heterotopic ossification [10].

While a gold standard for treatment of this condition does not currently exist, success with a variety of interventions has been reported, including both prophylactic and therapeutic options. Interventions to decrease the risk of such formation may include proper limb positioning, maintaining joint range, frequent monitoring of joint mobility, and even radiation [11]. Therapy focusing on range of motion and mobilization, bisphosphonates, NSAIDs, shock wave therapy, and even surgical intervention once bone is mature has been used with varying results [12–17]. Cochrane reviews of various treatments have been withdrawn recently due to being out-of-date (prior findings noted NSAIDs may reduce risk of heterotopic bone formation, but a second review noted a lack of sufficient evidence to recommend specific pharmacological interventions) [7].

In three of five cases presented in this series, a bisphosphonate (etidronate) was used as monotherapy in a treatment role rather than a prophylactic role, with overall improvement in patients’ self-reported pain symptoms and activities of daily living. Limitations of these case reports include limited outpatient assessment after discharge from acute rehabilitation and lack of objective outcome measurements to validate subjective improvements. Further research into the pathophysiology, prevention, and definitive treatments for heterotopic ossification is certainly needed.

**CONCLUSION**

Heterotopic ossification is a phenomenon that can easily go unrecognized in at risk patients. These cases demonstrate the wide variety of patients at risk of developing heterotopic ossification. We hope that this case series will promote further exploration of heterotopic ossification. We also hope this series will serve as a reminder for clinicians to include heterotopic ossification in their differential diagnosis when pain and fever occur in these settings.

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**Author Contributions**

Donald Hamby – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Brian Chau – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Mickey Lui – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Sarah Humbert – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Scott Strum – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Brian Kim – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Calvin Fesler – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Conflict of Interest

Authors declare no conflict of interest.

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