review

Heterotopic ossification: radiological and pathological review

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Background. Heterotopic Ossification (HO) is a common condition referring to ectopic bone formation in soft tissues. It has two major etiologies, acquired (more common) and genetic. The acquired form is closely related to tissue trauma. The exact pathogenesis of this disease remains unclear; however, there is ongoing research in prophylactic and therapeutic treatments that is promising.

Conclusions. Due to HO potential to cause disability, it is so important to differentiate it from other causes in order to establish the best possible management.

Key words: heterotopic ossification; radiology; pathology

Introduction

Heterotopic Ossification (HO), also known as paraosteoarthopathy, myositis ossificans, and heterotopic calcification[1] among others, is a commonly occurring condition referring to ectopic bone formation in soft tissues. HO can be subdivided in to two major types, acquired and genetic, with acquired being the most predominate. Acquired HO is closely related to tissue trauma and can be seen after joint surgery, musculoskeletal trauma, central nervous system injury, and even burns.[2] HO develops in up to 44% of patients undergoing hip arthroscopy or replacement, 10-20% of those with CNS injury, and 4% of those with burns covering greater than 30%.[3-10] Many cases of HO lead an indolent course, however severe cases can cause inflammation, pain, immobility and functional impairment.[11] Due to its potential to cause disability, it is imperative to be able to distinguish HO from other etiologies including tumoral calcinosis, osteos arcoma, or dystrophic calcification to provide adequate treatment.

Pathophysiology

Acquired HO can be broadly categorized in to three etiologic subtypes: neurogenic from central nervous system injury, orthopedic covering fractures, fixations, joint replacements, *etc.*, and trauma related to burns and high velocity impacts.[3] The formation of HO is tied to the underlying inflammatory process, which can even be demonstrated in genetic cases of HO where patients report prodromal symptoms of pain, swelling, and erythema prior to ectopic bone formation.[12] Trauma-induced HO is also correlated with the severity of the trauma, infection, total burn coverage[13] and cytokine concentration in affected tissues.[3,14] As a result, the most frequently used prophylactic medications are nonsteroidal anti-inflammatory drugs.[15] However, the underlying mechanisms for HO formation are less

clear. Literature has suggested multiple sources for the formation of HO, pointing to muscle satellite cells[16], smooth muscle cells[17], and even endothelial cells.[18] Although the exact cellular origin is debated, it is commonly accepted to be multipotent cells in the local tissue. The requirements necessary for HO formation include having an inducing agent, an osteogenic precursor, and a permissive environment for osteogenesis[19,20] which when met leads to proliferation and formation of bone.[21] Bidner *et al.* have proposed that failure to regulate the immune system or inflammatory response lead to the release of inciting agents that lead to HO.[19,22] Further investigations by Salisbury *et al.* and Kan *et al.* have implicated bone morphogenic protein type 2 (BMP-2) as a pro-inflammatory agent by stimulating release of substance p and calcitonin gene-related peptide from sensory nerves.[23,24] Further investigations support BMP's role in HO formation leading to targeted therapies.[3,21] Other suggested contributory factors include prostaglandin (specifically PGE-2), tissue hypoxia, and imbalance of parathyroid hormone and calcitonin.[25] A review performed by Cholok *et al*. showed multiple potential contributory cell lineages with likely varying signaling pathways, highlighting the current lack of understanding in HO formation.[3] The mechanisms of HO formation remain vague and need further investigation.

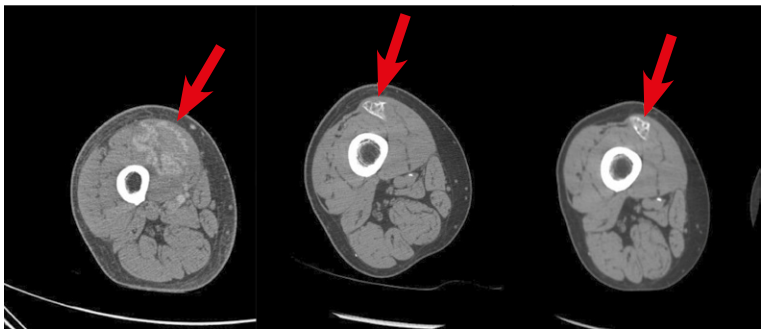

FIGURE 1. Progression of Heterotopic Ossification from presentation (left), 4 months (middle), and 8 months (right). Axial CT with contrast depicts initial hyperemia with increasing calcification at the site of injury with eventual outer cortical and inner cancellous bone formation.

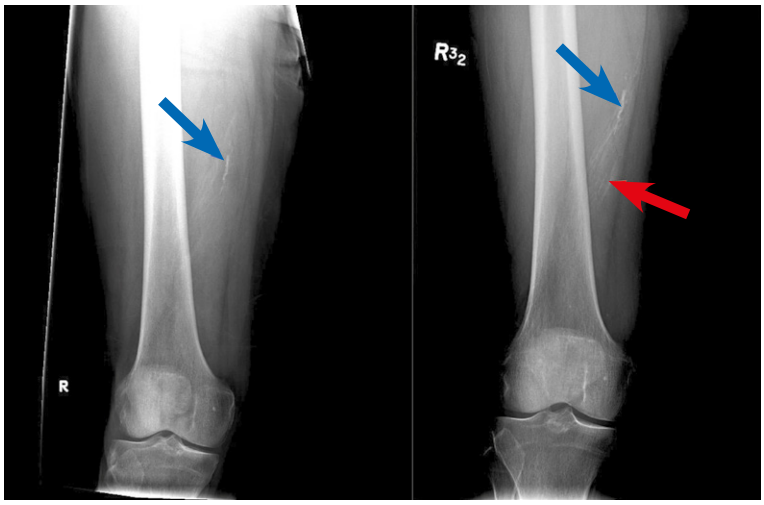

FIGURE 2. AP X-rays show previous vascular calcifications (Left-blue arrow) with no apparent masses at the site of injury at presentation. At 4 months follow up, there is increased calcifications noted (blue arrow) with expansion to the adjacent soft tissue area (red arrow) both are consistent with Heterotopic Ossification.

Clinical presentation and diagnosis

Patients presenting with HO typically complain of inflammatory symptoms including pain, swelling, erythema, and warmth along with joint immobility, which appear anywhere from 3 to 12 weeks after the precipitating event.[11,25-28] The most common sites of occurrence, in decreasing order, are the hips, knees, shoulders, and elbows.[25,27] The gold standard for diagnosing HO is through imaging studies, mainly x-ray and computerized tomography (CT).[3] The downfall to these types of imaging is that they are not able to detect calcifications for at least 6 weeks after the inciting trauma.[25,29] Three-phase bone scintigraphy is the most sensitive method for detecting HO, with the earliest detection being 2.5 weeks post trauma.[25,30] They are also effective in monitoring HO progression and determining the appropriate time to stage surgical intervention.[25,26,30] Activity on bone scans usually peaks a few months after the inciting event and returns to baseline by 12 months.[25]

Early screening methods used before imaging studies include alkaline phosphate levels and 24-hour PGE2. Alkaline phosphate levels can be increased two weeks after trauma, reaching 3.5 times baseline by 10 weeks, and then returning to baseline by 18 weeks. A rapid increase in 24-hour PGE2 urinary secretion has also been shown to suggest HO and would indicate further imaging studies.[31,32]

Upon detection with imaging, biopsies have been suggested to confirm diagnosis; however, current recommendations are to perform follow up imaging in four weeks to confirm along with a history of trauma to the region.[33]

Radiography and classification

A soft tissue mass is the earliest finding of HO on imaging, it is often depicted as a peripheral zone of mineralization in acquired cases.[33] With time,

these outer regions can mature in to a peripheral cortex with a well-defined cancellous bone interior detecTable by CT (Figures 1-2 and 3).[29,33] CT and x-ray (Figure 4) imaging remain the gold standard for diagnosis due to their ability to detect immature bone formation and relatively cheap cost.[3,29] In the acute phase of HO, there is increased vascularization and tissue density, which can be detected on Magnetic Resonance (MR).[34] This region appears isointense or hyperintense to muscle on T1 and hyperintense on T2 weighted images with pronounced surrounding inflammation.[34,35] As the rim of calcification forms, signal void begins to appear on the periphery on all sequences.[35,36] During this maturing phase, MR imaging results in non-specific findings and heterogenous signal that mimics many other pathologic processes.[29,37] Once mature, HO presents as cancellous fat that is hyperintense on T1 and T2 weighted images outlined by the hypointense cortical bone[29] and can be considered diagnostic. Therefore, when MR detects mature HO, no further imaging is necessary. On the other hand, early MRI can give us a great advantage in excluding other differential diagnosis possibilities, as we can observe the "striate pattern" and "checkerboard-like pattern" appearance in T2-WI and contrast-enhanced MRI images[38] or it can be detected by displacing the fascial planes, especially at the periphery of the lesion.[39] Recognizing these MRI patterns in HO could be very beneficial in early phases as it commonly misdiagnosed as osteomyelitis or even malignancy e.g. sarcomas.[40-42]

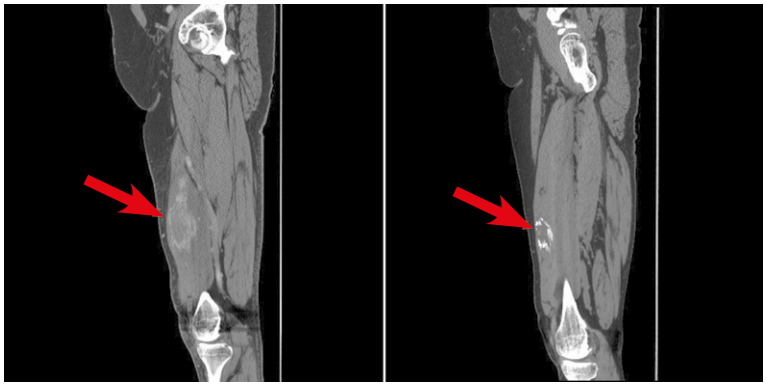

FIGURE 3. Heterotopic Ossification shown with initial hyperemia without calcification at presentation (left- red arrow) with increasing organized calcification seen after 4 months on Non-contrast CT (Right-red arrow)..

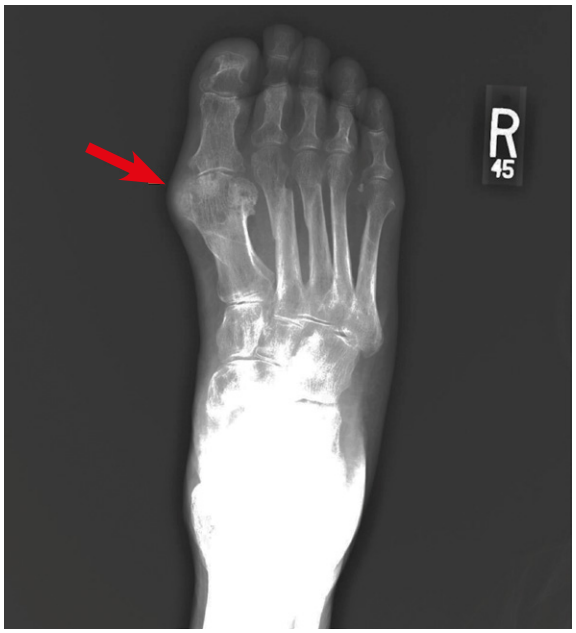

FIGURE 4. Severe gout presenting on the first metatarsophalangeal joint. AP X-ray of the right foot shows a medial pararticular calcified soft tissue mass at the level of the first metatarsophalangeal joint (red arrow), resulting in adjacent intraosseous erosions with sclerotic borders.

Ultrasonography (US) is proved to be a sensitive imaging modality in soft tissues lesions and calcifications[43,44] it is also safe, low-cost, easy, repeatable and a very useful tool in diagnosing and follow up of HO.[45] US has the great advantage of bedside application, which is very important in HO giving that a great number of patients are already bed-ridden.[45,46] Qing Wang *et al.* discussed a new concept for monitoring the trauma-induced HO. The study gives a guidance to the orthopedist to modify the treatment and make an individualized rehabilitation program. They have shown that the grey-scale values are different during the phases of HO maturation, and so it allow for a quantitative assessment during the rehabilitation of HO.[47]

Staging of HO is commonly done using the Brooker classification (Table 1), which was initially developed using anteroposterior radiographs of the hip.[9] There has been some criticism of this classification as anteroposterior radiographs cannot distinguish between bridging or overlapping calcifications in the anterior-posterior plane.[48] To simplify and reduce variability, Della Valle *et*

TABLE 1. Booker classification of heterotopic ossification[9]

Class 1	Islands of bone within the soft tissues about the hip
Class2	Bone spurs from the pelvis or proximal end of the femur, leaving at least one centimeter between opposing bone surfaces.
Class 3	Bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than one centimeter.
Class 4	Apparent bone ankylosis of the hip

TABLE 2. Della Valle classification of heterotopic ossification[49]

Class 1	Absence of HO or islands measuring <1 cm in length
Class 2	Islands >1 cm or spurs leaving at least 1 cm between femur and pelvis
Class 3	Spurs leaving <1 cm between opposing surfaces or bony ankylosis

TABLE 3. Schmidt and Hackenbroch classification of heterotopic ossification[50]

Region 1	Heterotopic ossifications strictly below tip of greater trochanter
Region 2	Heterotopic ossifications below and above tip of greater trochanter
Region 3	Heterotopic ossifications strictly above tip of greater trochanter
Grade A	Single or multiple heterotopic ossifications < 10 mm in maximal extent without contact with pelvis or femur
Grade B	Heterotopic ossifications > 10 mm without contact with pelvis but with possible contact with femur; no bridging from femur to proximal part of greater trochanter, with no evidence of ankylosis
Grade C	Ankylosis by means of firm bridging from femur to pelvis

al. (Table 2) created a modified classification using only three distinct grades.[49] A third and more comprehensive criteria was established by Schmidt and Hackenbroch (Table 3) with the goal of classifying HO while considering ossification within the region of surgical approach.[50] From these classifications, an important distinction for reporting and assessing severity is determining whether the space -between two opposing bone surfaces- is greater than or less than one centimeter.[9,49,50]

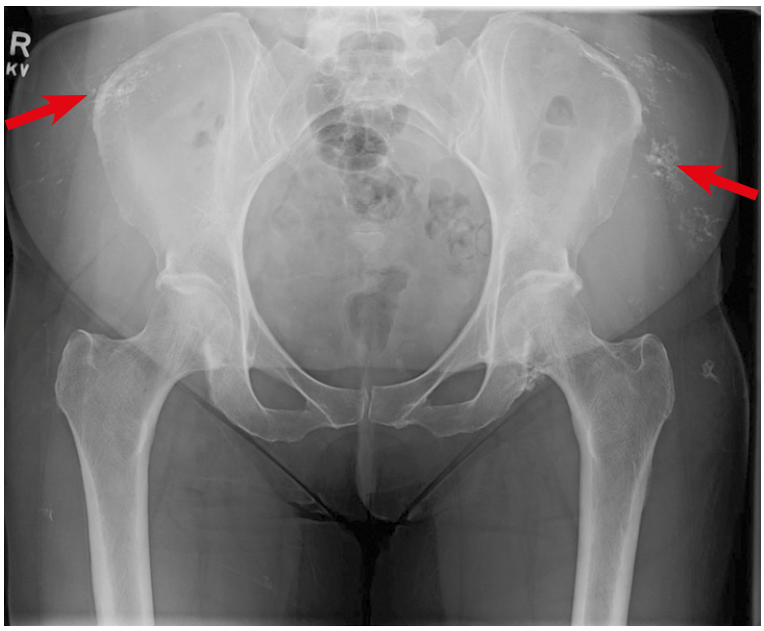

FIGURE 5. Dystrophic calcifications secondary to dermatomyositis are seen in the peripheral soft tissue (2 red arrows). They appear as hazy ill-defined opacities on plain film.

Differential diagnosis

Many types of pathologies can imitate HO clinically or radiographically. It is vital to understand the similarities and differences of these mimetics when considering the diagnosis of HO. A few differential diagnosis that should be considered are briefly discussed below.

Dystrophic calcification

Dystrophic calcification (DC) is the calcification that occurs in soft tissue post inflammation and damage. The mechanism of action is thought to be either disruption of cell membranes during trauma allowing calcium to enter and subsequently be concentrated in the mitochondria or by creating an acidic environment in the tissue that lacks calcification inhibitors.[51]

It is well documented to occur in cases of collagen vascular diseases like dermatomyositis (Figure 5), systemic lupus erythematosus, and scleroderma[52], but has also been identified in other disease processes.[51] On plain film, DC appears as amorphous calcification with a hazy ill-defined appearance that can increase in density over time.[53] CT will similarly show peripheral amorphous hyperdensities, with MRI showing hypointense signals in T1 and T2 weighted images (Figure 6).[54]

The distinguishing difference between DC and HO is organization. DC and HO are virtually indistinguishable on plain films, CT, or MRI early in the disease process as mineralization occurs. HO will begin to organize and ossify over the course of months in to lamellar bone while DC will remain as amorphous, non-ossified calcifications.[55]

Chondrocalcinosis

Chondrocalcinosis is calcification within fibrous or cartilaginous structures and is frequently associated with calcium pyrophosphatase disease (CPPD).[56] In cases of CPPD, there is usually acute, painful inflammation of a joint, often the knee, where calcium phosphate crystals are deposited.[57] Microcrystals can then impregnate cartilage causing arthritic symptoms, which can range from mild to severe with joint destruction.[57] On plain films, this appears as a dense line within hyaline cartilage that runs parallel to the articular surface.[56] CT has excellent sensitivity and specificity in detecting chondrocalcinosis and can better visualize the linear hyperintense calcifications (Figure 7).[56] There is often a concurrent degenerative joint disease with

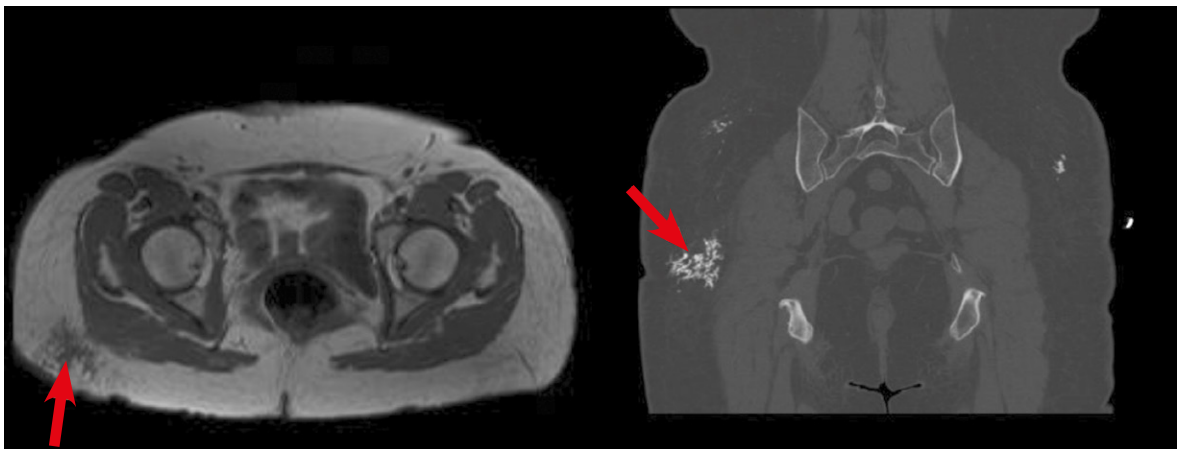

FIGURE 6. T1 weighted non-contrast MRI (left-red arrow) of dystrophic calcifications show hypointense signal in patchy patterns. These appear as calicified hazy patches on CT (right-red arrow).

joint space narrowing and large osteophyte formation.[58] The linear deposition contrasts with HO, which presents as a peripheral circumferential calcific mass on both plain films and CT with minimal intra-articular involvement. MRI has little utility in diagnosing Chondrocalcinosis, as the calcifications are not well visualized in tissues.[56]

Tumoral calcinosis

Tumoral calcinosis (TC) refers to a syndrome characterized by calcium salt deposition in peri-articular soft tissue.[59] A major component of TC is hyperphosphatemia secondary to genetically acquired decrease in phosphate secretion[59-61] or chronic renal failure and resulting hyperparathyroidism.[59] Patients present with joint pain, swelling, or immobility most commonly in the hip, elbow, shoulder,

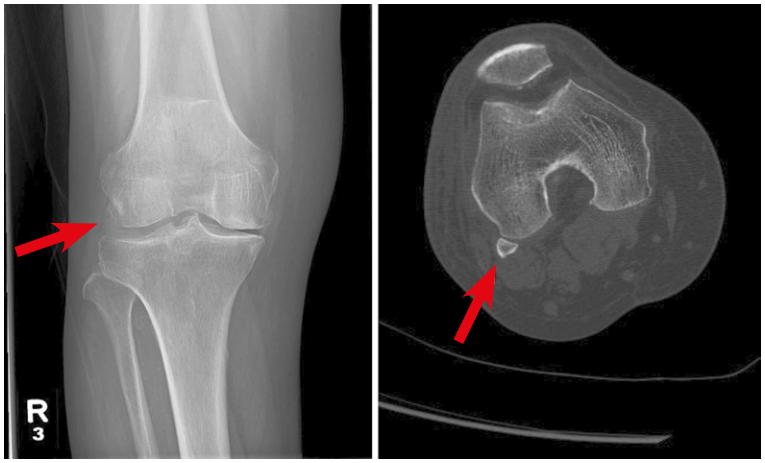

FIGURE 7. Calcium Pyrophosphate Deposition disease can lead to calcification of intra-articular cartilage. There is opacification of the lateral joint space on plain film (left-red arrow) and a more clearly defined mineralization seen near the lateral condyle on CT (right-red arrow).

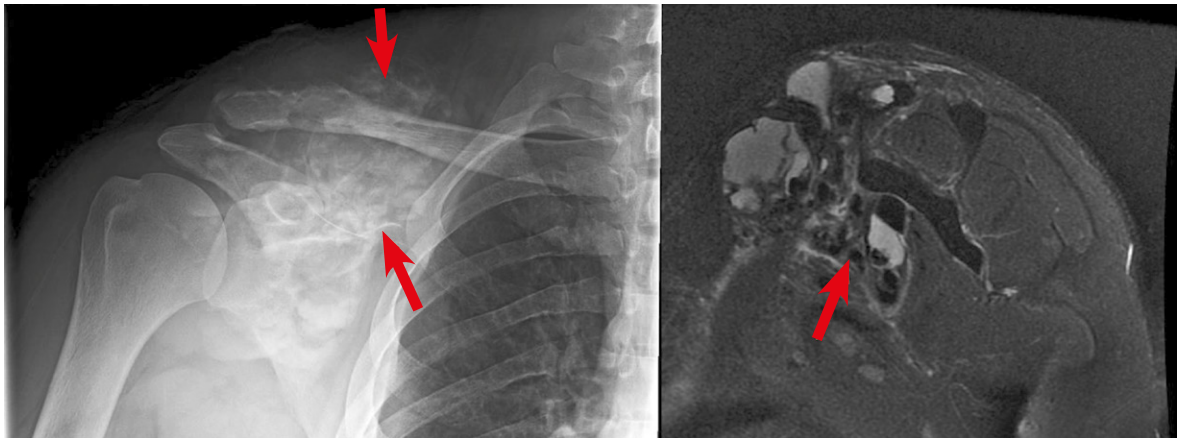

FIGURE 8. X-ray of the (left- 2 red arrows) shoulder show opacified cystic, lobulated peri-articular lesions in Tumoral Calcinosis. Coronal MRI T2 sequencing (right-red arrow) reveals hypointense lesions with septal enhancement, hyperintense fluid filled cavities and fluid –fluid levels consistent with sedimentation

foot, or wrist.[59,62-64] Unlike HO, TC lesions grow slowly over the course of several years.[65] Plain radiographs, ultrasound and CT can be used for diagnostic imaging showing fluid filled, lobulated, cystic calcifications in peri-articular tissue.[66] T1 and T2 weighted MRI show a hypointense lesion with septal enhancement (Figure 8). HO is not cystic in nature and lacks the lobulated pattern on both CT and MRI. HO also presents with hyperintense signal centrally with a hypointense cortical shell on T2 weighted images. Management of TC can be clinically determined based on symptoms and size of calcinosis with surgical or needle decompression as most common intervention.[66]

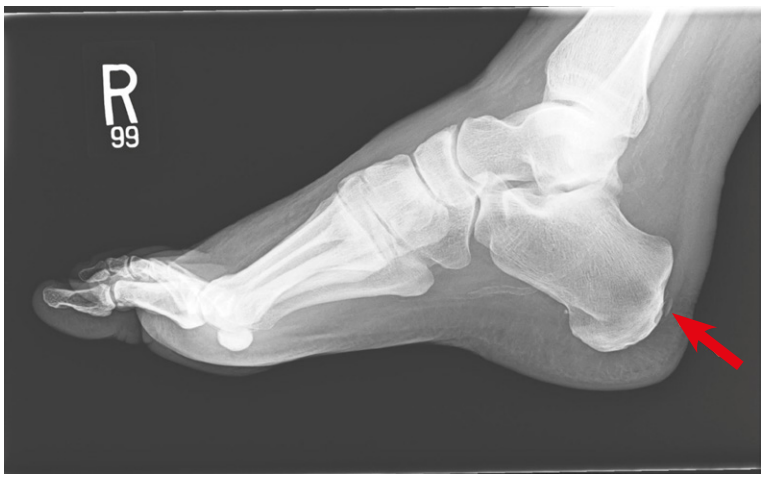

FIGURE 9. An avulsed piece of bone is seen on the posterior aspect of the calcaneus secondary to trauma (red arrow).

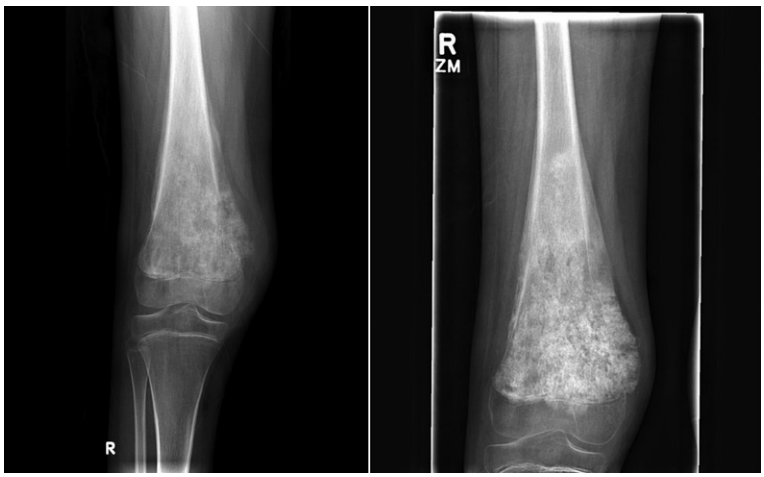

FIGURE 10. The "sunburst" appearance with cloudlike density of untreated Osteosarcoma is observed in the distal femur (left-red arrow). After chemotherapy, the lesion ossifies and becomes increasingly opaque on plain film (right-red arrow), consistent with positive therapeutic response).

Avulsion fracture

An avulsion fracture (AF) is the separation of a bone fragment at the site of tendon attachment, often occurring after a traumatic injury. Patients with this injury typically have a definite history of trauma accompanied by pain, swelling, and loss of joint function.[67] Findings on imaging can be seen immediately post trauma, depicting sharply delineated bone fragments (Figure 9). Large avulsed fragments can appear identical to matured HO, therefore having a clinical history is important. HO will not be identifiable on film until weeks after the inciting trauma and will not mature in to cortical bone for many months.[25] CT of avulsion fractures helps delineate fracture sites and show displaced hyperdense cortical bone.[67] HO can be distinguished from AF on CT, showing a ring of hyperdense cortical bone with a hypodense interior.[29,33] MRI may be useful in detecting local tissue damage seen in avulsion fragments; however, findings are consistent with inflammation and non-specific.[67]

Primary osteosarcoma

Osteosarcomas (OS) are the most common primary bone tumor, developing from uninhibited osteoid production by malignant mesenchymal cells.[68] Patients present with localized pain and swelling, which then proceeds to joint immobility. This type of tumor is commonly seen in the metaphysis of long bones, with incidence being the distal femur, proximal tibia, and then proximal humerus.[68,69] On plain radiographs, these can present as osteoblastic, osteolytic, or with mixed appearances, and have patchy calcifications from newly developing bone in surrounding soft tissue.[68] It is commonly described as a "sunburst" appearance or as having cloudlike density (Figure 10).[70] CT imaging is highly sensitive to calcification and useful in showing the amorphous osteoid formation in OS, which can help distinguish it from organized circumferential osteoid formation in HO. MRI shows heterogenous signal intensities on T1 and T2 sequencing due to a mixture of amorphous osteoid, hemorrhage, and necrosis.[70,71] Radiographs can be correlated with a low signal intensity on T1 imaging and hyperintensity on STIR imaging indicating mineralized matrix deposition with small periosteal reaction. Other findings include cortical bone destruction and marrow invasion not typically seen with HO.[71]

Tophaceous gout

Gout is a type of inflammatory arthritis caused by the deposition of monosodium urate crystals in joints and surrounding tissue.[72] Clinically, this presents as acute onset of pain and swelling at the site of deposition which is typically seen in the feet and knees but can also be seen elsewhere.[72] Early radiographic studies can often be negative, however in chronic gout patients, punched erosions with well-defined sclerotic borders can form extra marginally, articularly, or para-articularly with preservation of the joint space.[72,73] In severe cases, extreme bone destruction can occur with large periarticular lesions, joint space widening, and concurring osteoarthritis.[72-74] Tophi on CT are seen as discrete masses with a higher intensity than adjacent soft tissue.[75] CT is also useful in defining well-demarcated erosions with overhanging osteophytes seen in gout.[75] MRI is only beneficial in identifying soft tissue abnormalities around affected joints rather than tophi themselves, leading to low specificity and utility.[75] When seen, tophi appear with decreased signal intensity on T1 weighted images and heterogeneous signal on T2.[75] HO can be distinguished from tophaceous gout on x-ray and CT by lack of intraosseous erosions, peripheral calcifications in the soft tissue, and formation of cortical bone. MRI is not useful in distinguishing between the two unless the HO is mature, when complete lamellar bone is seen.

Calcific tendonitis

Calcific Tendonitis refers to the condition of calcium deposition in tendons.[76] This is clinically depicted by chronic pain with activity, tenderness, swelling, and joint immobility that is commonly localized to the rotator cuff tendons.[76,77] The etiology remains unknown; however, severity has been associated with endocrine diseases.[78] Pathology can be noted by standard AP radiograph with internal and external rotation views showing dense homogenous calcification typically noted proximal to the greater tubercle (Figure 11).[79] Ultrasound, used to evaluate rotator cuff injury, can present with hyperechoic lesions with reproducible pain in palpation during ultrasound therapy.[80] Calcific tendonitis can also be viewed with susceptibility-weighted imaging, which presents as a hyperintense lesion at tendon insertion site with occasional central hypointensity. It lacks the well-defined shape of HO and the hyperintense core seen on T1 weighted images.[81]

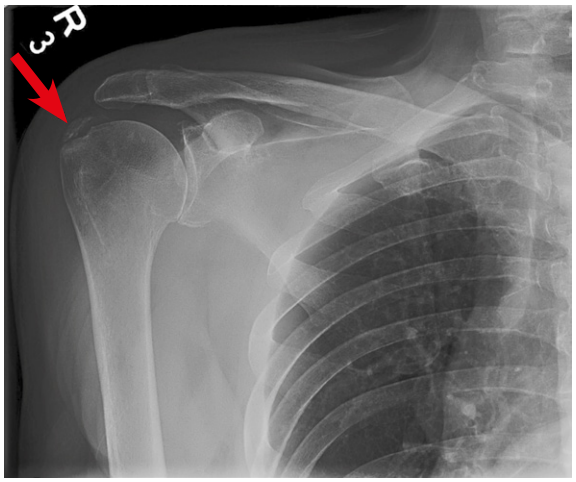

FIGURE 11. Opaque linear coarse calcification along the expected location of the supraspinatus tendon insertion onto the greater tubercle of the humerus (red arrow), consistent with Calcific Tendonitis.

Fibrodysplasia Ossificans Progressiva

Fibrodysplasia Ossificans Progessiva is an extremely rare genetic form of HO in which patients repair mechanism ossifies fibrous tissue leaving patient permanently frozen secondary to minor trauma.[82] Patients initially present with characteristic malformations of the large toes at birth with painful soft tissue swelling and ectopic bone formation within the first decade of life.[82-84] Laboratory changes include increased alkaline phosphatase and urinary basic fibroblast growth factor during acute episodes. Radiographic imaging shows extensive heterotopic bone formation diffusely with no specific pattern and ankylosis of adjacent joints with heterotopic bone formation.[82] MRI can show heterotopic bone formation with underlying edema and subtle soft tissue changes indicating pre-osseous lesions, noted as hyperintense lesion on fat suppressed T2 imaging.[85] CT imaging can be used for volumetric analysis of ossification that is unattainable via radiographs or MRI, showing the extent of joint ankylosis with 3D rendition and assessment of severity via Lederson grading scale.[85] This condition can be distinguished from traumatic HO by early onset and severe disseminated ossification.

Treatment

Treatment for HO is divided in to prophylaxis for high-risk patients and management of already formed HO. Due to the large variability in etiology and underlying mechanisms for HO and individu-

alized patient risk factors, there is little agreement on appropriate treatment regimens. Commonly used prophylaxis includes NSAIDs, localized low dose radiation, or a combination there-of with the most popular being NSAID alone.[86,87] Prophylactic NSAIDs have shown to reduce the occurrence of ectopic bone formation when given peri-operatively compared to placebo at the expense of medication side effects such as gastrointestinal ulcers, bleeding, and delayed bone healing.[88,89] Although there is a decrease in HO formation, NSAIDs had no effect on pain or physical function compared to placebo.[88,90,91] NSAIDs target pro-inflammatory prostaglandins, which have been shown to be integral to osteogenesis and are thought to have some effect by suppressing the migration and proliferation of mesenchymal cells.[21,92,93] The NSAID of choice is the non-selective cox inhibitor indomethacin.[94] Cox-2 specific inhibitors have been suggested to reduce side effects associated with nonselective cox inhibitors; however, their cardiovascular side effects and lack of safety with routine use limit their use.[15]

Coventry *et al.* first established radiation therapy (RT) as an effective treatment in 1981, and further studies by Childs *et al.* and Chao *et al.* confirmed its benefits.[95-97] In the retrospective cohort study by Childs *et al.* covering 263 patients whom experienced traumatic acetabular fractures, 5.3% of patients receiving RT also developed ectopic bone formation compared to 60% of patients without any treatment. The drawbacks to RT include potential side effects such as carcinogenesis, bone disunion, and oligospermia as well as total cost.[15] Strauss *et al.* determined that the total cost of RT was approximately 45 times higher than that of NSAIDs.[98] The high cost of RT limits its utility, especially considering it has not been shown to be more effective than NSAID therapy.[99] Other therapies currently under development and clinical testing include BMP antagonists, selective ALK receptor inhibitors, Noggin protein delivery, and retinoic acid.[21]

Surgical management currently remains the only effective treatment for formed ectopic bone. Indications for surgery include symptomatic disabilities and radiographic evidence showing the cessation of bone growth.[3] Surgery should not be performed until 12 to 18 months after HO formation to allow maturation of the lesion and patient's tissue has had time to recover to decrease intraoperative complications and HO reoccurrence.[28,100] Although efficacious, surgery inherently causes tissue trauma, which can simulate the same inflammatory conditions for HO formation and is therefore complicated by high reoccurrence rates.[101]

Conclusions

Heterotopic ossification is a commonly seen condition occurring secondary to trauma that can cause mild to severe disability in patients. The exact pathogenesis of this disease remains unclear; however, there is ongoing research in prophylactic and therapeutic treatments that is promising. Distinguishing between HO and other mimetics can help clinicians better identify and improve patient care.

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