Pathophysiology of Heterotopic Ossification

Michael E. Zychowicz

Heterotopic ossification (HO) is a pathologic condition that leads to the development of bone within nonosseous soft tissues. A common site for HO development is at the hip. The bone that forms is believed to develop through stimulation by cellular mediators and altered neurovascular signaling. Heterotopic ossification can be a debilitating disease leading to pain, edema, and stiffness. This only compounds already-debilitating comorbid conditions such as a spinal cord injury, head injury, or trauma. Several factors, including prostaglandin E2, bone morphogenetic protein, and the inflammatory process, are believed to contribute to the development of HO. The full scope of pathophysiology contributing to HO is not fully understood.

Introduction

Heterotopic ossification (HO) is a pathologic condition where patients develop bone formation within nonosseous tissues. A common site for HO development is at the hip. The bone that forms in tissues with HO is mature lamellar bone and is believed to be stimulated to develop through cellular mediators and altered neurovascular signaling (Keschner & Paksima, 2007). This condition has been described in children early in the medical literature in 1692 (Bossche & Vanderstraeten, 2005). Heterotopic ossification was later described by Reidel in 1883 and subsequently by Dejerne and Ceillier in 1918 as developing in soldiers who suffered spinal cord injuries (SCIs) in combat (Shehab, Elgazzar, & Collier, 2002). The physiologic process in the development of HO is not fully understood in the scientific literature.

Epidemiology

Several conditions have been correlated with the development of HO (see Table 1). Frequently, the bone that forms in patients with HO occurs following an SCI, musculoskeletal trauma, surgical intervention, or brain injury (Frassica, Sponseller, & Wilckens, 2006). For patients with these conditions, the hip is a very common site for the development of HO (Bossche & Vanderstraeten, 2005). Patients with SCIs have approximately a 20%–30% chance for developing HO. This typically will develop at a site that is distal to the SCI (Shehab et al., 2002).

Up to 35% of those patients with an SCI will develop a limitation in range of motion of the affected body part (Shehab et al., 2002). Between 70% and 97% of patients will have the hip as their primary site of HO development within 2–3 weeks following SCIs. Nearly 8% of patients will go on to develop ankylosis at the hip (Teasell et al., 2010). Following an SCI, there appears to be a relationship with the development of HO and experiencing muscle spasticity, a fracture, limited range of motion or greater than 2 weeks' loss of consciousness (Aubut, Mehta, Cullen, & Teasell, 2011).

In patients with a closed brain injury, HO occurs in approximately 10%–20% of patients. Nearly 10% of those who develop HO following a closed brain injury will also develop significantly limited range of motion at the affected joint (Shehab et al., 2002). Some of the most commonly affected joints of people who develop HO following a closed brain injury include the hip, elbow, and knees (Aubut et al., 2011).

There appears to be no difference in HO development when comparing racial groups. Males and females have an equal incidence of HO following some type of nerve injury. Nearly 20%–30% of those patients with a nerve injury will develop HO within 2–4 months (Bossche & Vanderstraeten, 2005; Frassica et al., 2006).

Patients with a greater degree of trauma have a greater risk for the development of HO. Only 3% of patients who have an elbow dislocation will develop HO. This is contrasted by nearly 20% of patients who will develop HO following a fracture and dislocation at the elbow (Keschner & Paksima, 2007).

Heterotopic ossification is a possible complication following total hip arthroplasty (THA). Males generally have a greater incidence of developing HO following a THA than females. The incidence of HO in patients with a THA ranges between 16% and 53% (Bossche & Vanderstraeten, 2005). Nearly 3% of people who develop HO following a THA will be severely disabled (Vigorita, 2008). Up to 90% of the patients who have a

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Table 1. Conditions Correlated With Heterotopic Ossification Development

Atherosclerosis	Tumors
Trauma	Spinal cord injury
Head injury	Infection
Bone marrow transplant	Joint arthroplasty
Burns	Spondyloarthropathies

Note. Adapted from *Orthopaedic Pathology* (2nd ed.), by V. J. Vigorita, 2008, Philadelphia, PA: Lippincott Williams & Wilkins.

THA following an acetabular fracture will develop HO at the hip (Bossche & Vanderstraeten, 2005).

The development of HO in children is generally less than that for adults. Children also frequently have a spontaneous resolution of their symptoms. Children with fibrodysplasia ossificans progressiva can potentially develop HO following administration of DTP immunization (Bossche & Vanderstraeten, 2005).

Some additional causes for HO include multiple sclerosis, sickle cell disease, hemophilia, tetanus, and burns. Some patients will experience an idiopathic development of HO. Patients can develop HO in the kidney, gastrointestinal tract, and uterus as well as following abdominal surgery (Shehab et al., 2002). Following abdominal surgery, the greatest incidence of HO occurs in men older than 55 years (Christofi, Raptis, Kallis, & Ambasakoor, 2008).

Risk Factors

Several risk factors increase the likelihood for developing HO. A history of prior HO increases a patient's risk for future development of HO (Bossche & Vanderstraeten, 2005; Keschner & Paksima, 2007). A possible unknown genetic cause may lead to an increased risk for the development of HO. Patients with ankylosing spondylitis, Paget's disease, heterotopic osteoarthritis, and disseminated idiopathic skeletal hyperostosis (DISH) have an increased risk of developing HO (Keschner & Paksima, 2007). A possible link may exist between developing HO and human leukocyte antigen B18, B27, and DW7 (Bossche & Vanderstraeten, 2005).

Surgical procedures can increase a patient's risk for developing HO (Xue et al., 2011). Patients have an increased risk for development of HO following a THA or trochanteric osteotomy. Not only does the surgical procedure increase the risk for HO, but the surgical approach can increase the risk. A lateral approach to THA appears to have a greater risk for HO development (Vigorita, 2008).

Some factors lead to a decreased risk for the development of HO. Older patients have a decrease in osteogenesis with a potential for a decreased risk of developing HO. Patients who have collagen synthesis injuries can have a decreased risk for HO. This may occur with corticosteroid or penicillamine use. Finally, aluminum has been demonstrated to decrease endochondral bone formation that may decrease the risk of HO formation (Vigorita, 2008).

History and Physical Findings

Patients who develop HO will typically complain of somewhat nonspecific symptoms. Erythema, warmth, edema, fever, and unexplained increasing pain are some of the most common initial symptoms (Frassica et al., 2006; Keschner & Paksima, 2007). Nearly 80% of patients who develop HO will have a rather benign course with symptoms resembling an inflammatory disorder, cellulitis, phlebitis, or a deep vein thrombosis (Bossche & Vanderstraeten, 2005; Shehab et al., 2002).

The signs and symptoms a patient with HO complains of will typically begin 1–3 months following a precipitating injury. The patient who develops HO will progress from the initial symptoms of swelling to develop a palpable mass as well as induration and stiffness (Bossche & Vanderstraeten, 2005). Ossification within tissues may lead to muscle pain, spasm, and guarding (Frassica et al., 2006).

Loss of function, tissue breakdown, limited motion, ankylosis, nerve compression, and vascular compression are possible complications of the ossification that occurs with HO. Ossification can lead to compression of vascular structures and subsequent increased hydrostatic pressure and edema or an effusion distal to the ossified lesion (Bossche & Vanderstraeten, 2005). Ankylosis can occur in approximately 10% of patients with HO, leading to functional difficulties with mobility and activities of daily living (Keschner & Paksima, 2007; Shehab et al., 2002). Some patients may complain of neuropathic pain, numbness, tingling, and loss of function due to nerve entrapment within the HO (Shehab et al., 2002).

Diagnostic Testing and Imaging

Approximately 2–3 weeks following the onset of HO, serum alkaline phosphatase (ALP) will be elevated (Frassica et al., 2006). Alkaline phosphatase is a glycosylated protein, or glycoprotein, that is produced by bone, renal, hepatic, intestinal, and placenta cells. In bone, ALP is located primarily in the plasma membrane of osteoblasts (Vigorita, 2008). Serum ALP is generally produced and released by osteoblasts during the bone formation phase of the bone turnover cycle. Pathologic conditions that increase bone formation or bone turnover will increase serum ALP. These include conditions such as Paget's disease, fracture healing, osteoblastic tumor, osteomalacia, rickets, hyperparathyroidism, and HO (Jacobs, DeMott, & Oxley, 2004).

Prostaglandins (PGs) are typically thought of as a major component of the inflammatory process leading to pain stimulation, neutrophil chemotaxis, and vascular permeability. There are several subgroups of PG, including PGA, PGB, PGD, PGE, and PGF (McCance, Heuther, Brashers, & Rote, 2010). Prostaglandins play a role in both bone reabsorption and bone formation. These actions are dependent upon several factors, including receptor and signaling pathway activation. Prostaglandins can contribute to the bone formation seen in patients with HO or a healing fracture. Conversely, PGs will contribute to the bone loss in patients who have a lytic metastatic bone cancer or inflammatory disease

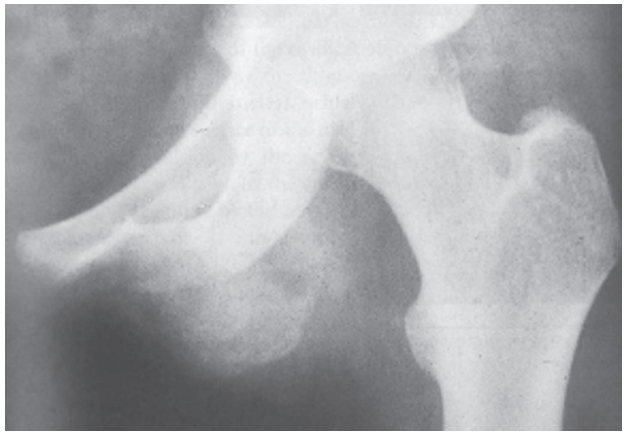

Figure 1. X-ray demonstrating early bone formation of heterotopic ossification. From *Orthopaedic Pathology* (2nd ed.), by V. J. Vigorita, 2008, Philadelphia, PA: Lippincott Williams & Wilkins.

Figure 2. Cancellous and lamellar bone tissue of heterotopic ossification. From *Orthopaedic Pathology* (2nd ed.), by V. J. Vigorita, 2008, Philadelphia, PA: Lippincott Williams & Wilkins.

such as rheumatoid arthritis (Blackwell, Raisz, & Pilbeam, 2010).

In patients who have HO, there is an increased urinary excretion of prostaglandin E2 (PGE2), which is thought to be from increased PGE2 production subsequently stimulating the bone formation characteristic of HO (Teasell et al., 2010). A 24-hour urinary PGE2 may be a useful early detection test to identify patients who have suspected HO. A decrease in urinary PGE2 can also assist providers in identifying the effectiveness of the treatment regimen (Bossche & Vanderstraeten, 2005).

A bone scan is a test that evaluates bone metabolism by way of bony uptake of an injected radioisotope. Patients who have HO have an increase in bone deposition at a focal area. Those patients will have an increased uptake of radioisotope and a positive bone scan (Frassica et al., 2006). A three-phase bone scan is thought to be more sensitive in assisting to diagnose a patient with HO earlier than with a plain radiograph (Teasell et al., 2010). A patient will typically have a positive bone scan within 2–4 weeks after the onset of developing HO. In addition, because a bone scan evaluates metabolic bone activity, it can be used to evaluate the efficacy of treatment in slowing bone formation (Bossche & Vanderstraeten, 2005).

A plain x-ray is not very useful in identifying new bone formation as early as a bone scan. An x-ray will not see new bone formation until 3–6 weeks after its formation (Frassica et al., 2006). An x-ray that shows early bone formation will demonstrate nondistinct and poorly defined margins (see Figure 1) of that bone formation (Keschner & Paksima, 2007).

Both magnetic resonance imaging and computed tomographic scan can be useful in the evaluation of HO. The use of computed tomography or magnetic resonance imaging is generally best late in the development of HO as a component of preoperative planning (Frassica et al., 2006; Teasell et al., 2010). These imaging studies may provide information about nerve and blood vessel entrapment to further assist with preoperative planning. An angiogram may also provide further information about vascular entrapment within HO (Bossche & Vanderstraeten, 2005).

Disease Classification

Several classifications exist for the classification of HO. Schmidt and Hackenbroch classification system is one method described in the literature to grade HO in patients who have evidence of the HO at the hip (Shehab et al., 2002). Other classification systems exist describing HO at other joints, such as the elbow (Keschner & Paksima, 2007).

The Brooker classification system is a method of grading HO specifically at the hip. This system describes five grades of HO dependent upon the degree of ossification (Xue et al., 2011).

- *Grade 0*: no ossification present.
- *Grade 1*: small bone islands are identified in the tissues around the bone.
- *Grade 2*: bone spurs are identified at the pelvis and/or proximal femur. There is more than 1 cm of space between the opposing bones.
- *Grade 3*: bone spurs identified at the pelvis and/or proximal femur. There is less than 1 cm of space between the opposing bones.
- *Grade 4*: ankylosis present at the hip.

Pathophysiology

Several conditions are believed to contribute to and allow for the development of HO. First, there must be an event to begin the process. Some of the most common conditions that can precipitate the development of HO include an SCI, musculoskeletal trauma, surgical intervention, or traumatic brain injury (Frassica et al., 2006). An agent must be produced or released following the instigating event that has the potential to initiate the development of HO (Christofi et al., 2008). Precursor cells with the potential to become the bone of HO must be present within a cellular environment that will support this change (Shehab et al., 2002).

The bone that forms with the development of HO is composed of both cancellous and lamellar bone tissue (see Figure 2). Within HO, bone marrow and vascular tissue develop (Bossche & Vanderstraeten, 2005). The formation of HO occurs within the connective tissue planes and not within muscle tissue. Microscopic examination of tissue surrounding HO demonstrates not only the connective tissue within which the HO developed, but also muscle fibers that have been compressed because of the outward growth and ossification of the lesion (Bossche & Vanderstraeten, 2005).

During the development of HO, undifferentiated tissues within the connective tissue planes are exposed to various initiating agents eventually leading to cellular differentiation toward the development of bone (Shehab et al., 2002; Vigorita, 2008). Mesenchyme is an undifferentiated loose connective tissue from which fibroblasts develop. A primary role of fibroblasts is to secrete collagen and extracellular matrix. The structural integrity of connective tissue is maintained by the collagen and extracellular matrix produced by fibroblasts (Vigorita, 2008).

A process of fibroblastic metaplasia occurs during HO development (Bossche & Vanderstraeten, 2005). Metaplasia refers to the cellular process of transforming one type of cell to another type of cell. This process can occur as a normal biologic process such as that occurs with chondrocyte ossification during bone growth. Metaplasia can also occur following chronic tissue injury or irritation such as that which occurs with bronchial epithelium and prolonged smoking (McCance et al., 2010).

During the development of HO, an area of fibroblastic metaplasia forms within the connective tissue plane. Subsequently, chondroblasts form, which eventually change to become osteoblasts. The osteoblastic tissue will form into HO. This will have lamellar and cancellous bone, haversian canals, vascular tissue, and marrow (Bossche & Vanderstraeten, 2005).

Bone morphogenetic protein (BMP) is an agent produced by the body, which has the potential to initiate the development of HO. The release of BMP is believed to be caused by several conditions, including immobilization, trauma, inflammation, venous stasis, and connective tissue disorders involving bony attachments (Shehab et al., 2002). A decrease in antagonists to BMP can also allow for and increased production and release of this induction factor. Follistatin and chordin are two such BMP antagonists (Christofi et al., 2008).

An increase in BMP can lead to an increase in osteogenic cell differentiation (Christofi et al., 2008). This inducing factor is a polypeptide that can stimulate the differentiation of mesenchymal cells to develop into chondrocytes and eventually osteoblasts (Shehab et al., 2002). This effect on cellular differentiation is clearly seen during normal postfetal cellular differentiation (Vigorita, 2008).

Inflammation contributes to the development of HO. Inflammation may be a result of tissue trauma but can also be a function of deinnervation that occurs with SCI. It is believed that inflammatory signaling may lead to inflammation, which can occur following an SCI and the loss of peripheral nerve signaling (Jones, Mollano, Morcuende, Cooper, & Saltzman, 2004).

Metaplastic changes leading to mesenchymal cells converting to osteoblastic cells are believed to be stimulated in part by the inflammatory process (Jones et al., 2004). Many cellular mediators are released during the inflammatory process. Both leukotrienes and PGE2 are released during the inflammatory process. They are both responsible for increased periosteal lamellar bone formation (Bossche & Vanderstraeten, 2005). Prostaglandin E2 is thought to stimulate mesenchymal cell differentiation to osteoblasts as well as contributing to angiogenesis and vascular formation within the HO (Aubut et al., 2011; Bossche & Vanderstraeten, 2005; Shehab et al., 2002).

Summary

Heterotopic ossification can be a debilitating disease leading to pain, edema, and stiffness. This only compounds an already-debilitating condition such as an SCI, head injury, or trauma. The full scope of pathophysiology contributing to HO is not fully understood. Several factors are believed to contribute to the development of HO including PGE2, BMP, and the inflammatory process. Basic research must continue to contribute to our understanding of the development of HO.

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