Heterotopic Ossification: Two Rare Forms and What They Can Teach Us

Frederick S. Kaplan, MD, Gregory V. Hahn, MD, and Michael A. Zasloff, MD, PhD

Abstract

Heterotopic ossification is characterized by the formation of normal bone at ectopic soft-tissue locations. Regardless of the etiology of heterotopic ossification, requisite pathogenetic conditions include an inductive signal capable of stimulating morphogenesis, a population of inducible osteoprogenitor cells, and a heterotopic environment conducive to osteogenesis. Two rare heritable and developmental forms of heterotopic ossification, fibrodysplasia ossificans progressiva and progressive osseous heteroplasia, provide valuable clinical and pathogenetic insights into heterotopic ossification in humans. A fundamental understanding of the developmental and molecular pathology of these disorders may lead to more effective strategies for preventing and treating heterotopic ossification in humans.

J Am Acad Orthop Surg 1994;2:288-296

The formation of bone where it is neither wanted nor needed can frustrate clinicians and patients, but it can also provide a unique perspective on the mechanisms by which bone formation occurs normally. There are numerous forms of heterotopic ossification, ranging from the common acquired posttraumatic and postsurgical forms to the exceedingly rare genetic and developmental forms. The genetic forms of heterotopic ossification provide the orthopaedic surgeon with a unique opportunity to discover the molecular basis of heterotopic skeletogenesis. Understanding the pathophysiology of these disorders will likely facilitate the development of more effective therapies for common forms of heterotopic ossification.

Etiology and Pathogenesis

There are many causes of heterotopic ossification. Acquired forms may be due to trauma, burns, infections, neoplasia, spondyloarthropathies, neurologic diseases, chronic venous insufficiency, and postsurgical complications. There are also rare heritable diseases (Table 1).

Factors involved in the regulation of normal osteogenesis have been implicated in the regulation of heterotopic ossification. Regardless of the etiology, the pathogenesis of heterotopic ossification involves three requisite conditions[1]: (1) an inductive signal, (2) a population of inducible mesenchymal stem cells, and (3) a heterotopic environment conducive to osteogenesis.

No definitive inductive factor has yet been identified in any of the naturally occurring forms of heterotopic ossification. The recent identification and successful cloning of the bone morphogenetic proteins (BMPs) suggest possible candidate molecules in the induction pathways of heterotopic ossification.[2,3]

A population of inducible mesenchymal stem cells is a second requirement.[4] To date, the clonal identity of inducible osteoprogenitor cells is uncertain,[4] but recent experimental data point to perivascular cells as possible candidates.[5]

Finally, the biochemical, cellular, histologic, and microvascular environment must be permissive to the ossification pathways at all stages of osteogenesis, from the earliest inductive event through remodeling of mature lamellar bone.[1]

Acquired Forms of Heterotopic Ossification

Common causes of heterotopic ossification include trauma, scars, burns, paraplegia, cerebral injury, poliomyelitis, and arthropathies.[6]

Dr. Kaplan is Chief, Molecular Orthopaedics and Metabolic Bone Diseases, Department of Orthopaedic Surgery, University of Pennsylvania School of Medicine, Philadelphia. Dr. Hahn is a Fellow in Molecular Orthopaedics, Department of Orthopaedic Surgery, University of Pennsylvania School of Medicine. Dr. Zasloff is Adjunct Professor of Orthopaedic Surgery and Genetics, University of Pennsylvania School of Medicine.

Reprint requests: Dr. Kaplan, Department of Orthopaedic Surgery, Hospital of the University of Pennsylvania, Silverstein 2, 3400 Spruce Street, Philadelphia, PA 19104.

Table 1
Etiology of Heterotopic Ossification

- Acquired forms
  - Injury
    - Central nervous system
      - Brain
        - Closed head trauma with coma
        - Cerebrovascular accident with hemiplegia
      - Spinal cord
        - Paraplegia
        - Quadriplegia
      - Lower motor neuron (poliomyelitis)
    - Soft tissue
      - Blunt trauma
        - Muscle hematoma
        - Joint dislocation
      - Postsurgical
        - Following total hip arthroplasty
        - Surgical scars
      - Osteoma cutis
        - Burns
        - Nevi
        - Idiopathic
  - Vascular
    - Chronic vascular insuÓciency
    - Aortic insuÓciency
  - Arthropathies
    - Ankylosing spondylitis
    - Psoriatic arthritis
    - Seronegative arthropathies
    - DiÏuse idiopathic skeletal hyperostosis
- Genetic and developmental forms
  - Fibrodysplasia ossiˆcans progressiva
  - Progressive osseous heteroplasia
  - Albright's hereditary osteodystrophy
  - Tracheopathia osteoplastica

(Adapted with permission from Brighton C [ed]: *Bone Formation and Regeneration*. Rosemont, Ill: American Academy of Orthopaedic Surgeons [in press].)

Myositis ossificans traumatica may develop following muscular hematoma from a sports-related injury. The ossification process is predominantly endochondral, and in its early stages may be mistaken pathologically for extraosseous osteosarcoma. Sarcomas, however, exhibit the most aggressive histopathologic changes at the periphery of the lesion, while immature heterotopic bone exhibits the most aggressive histopathologic changes at the center of the lesion.

Heterotopic ossification is commonly seen following spinal cord injury, cerebral injury, and poliomyelitis. Local factors, such as stasis, edema, swelling, and prolonged immobilization, are often cited as contributing factors. Attempts to isolate local or systemic inductive factors have not been fruitful.

Intravascular heterotopic ossification may occur in areas of calcified aortic plaques. Expression of BMP2 messenger RNA has been identified in the pericyte-like cells of the aortic wall, and BMP2 has been found in calcified atherosclerotic plaque. It appears that arterial ossification is a regulated process, possibly mediated by pericyte-like cells.[5]

Heterotopic ossification has been reported to occur in 8% to 12% of patients following total hip arthroplasty, but estimates as high as 20% have been reported. Clinically significant (limiting motion) heterotopic ossification following total hip arthroplasty occurs in 1% to 3% of cases. Commonly cited contributing factors include male gender, proliferative osteoarthritis, ankylosing spondylitis,[6] and diffuse idiopathic skeletal hyperostosis.

Ossification of spinal ligaments occurs commonly in patients who have seronegative spondyloarthropathies and may occur in association with diffuse idiopathic skeletal hyperostosis. The pathogenesis of ossification is unknown in all of these conditions.[6]

Genetic and Developmental Forms of Heterotopic Ossification

There are two rare genetic and developmental forms that are of interest to orthopaedic surgeons (Table 2) because of the insight they give into the molecular events accompanying heterotopic ossification. These forms are fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia (POH).

Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva is a progressively disabling genetic disorder characterized by congenital skeletal malformations of the toes and progressive endochondral heterotopic ossification in specific anatomic patterns.[7] This disorder is exceedingly rare, with a point prevalence of 0.6×10^{-6} according to a study from the United Kingdom.[8] There are approximately 100 known patients in the United States. Most cases of FOP appear to arise by spontaneous mutation, and no sexual, racial, or ethnic predilection has been observed. Although reproductive fitness is low and several large series of patients reported no familial transmission, autosomal-dominant transmission has been documented recently.[9]

Nearly all patients who have FOP have congenital malformations of the great toes[7,10] (Fig. 1). The most common malformation is a shortened great toe with a single or delta-shaped phalanx.[7] Other, more variable congenital malformations include short, broad femoral necks; clinodactyly; and abnormal cervical vertebrae with small bodies, large pedicles, and large spinous processes.[11,12] Progressive heterotopic ossification begins early in childhood, often during infancy, and first appears in the posterior axial region.

Table 2
Developmental Disorders of Heterotopic Ossification

Feature*	Fibrodysplasia Ossificans Progressiva	Progressive Osseous Heteroplasia
Gender distribution	M = F	F > M
Congenital papular rash	No	Yes
Congenital malformation of great toes	Yes	No
Brachydactyly, short stature, obesity, round facies, and mental retardation	No	No
Cutaneous ossification	No	Yes
Extensive heterotopic ossification of deep connective tissue	Yes	Yes
Predominant mechanism of ossification	Endochondral	Noninflammatory heteroplasia
Presence of hematopoietic marrow in mature heterotopic bone	Yes	Variable
Stringent developmental patterns of progressive ossification	Yes	No
Exacerbation by trauma	Yes	No
Hypocalcemia, hyperphosphatemia, and decreased urinary cAMP response to PTH	No	No
Serum alkaline phosphatase level	Usually elevated	Variable
Serum PTH level	Normal	Normal
Pathogenesis	Unknown	Unknown

* cAMP 5 cyclic adenosine monophosphate; PTH 5 parathyroid hormone.
(Adapted with permission from Brighton C [ed]: *Bone Formation and Regeneration*. Rosemont, Ill: American Academy of Orthopaedic Surgeons [in press].)

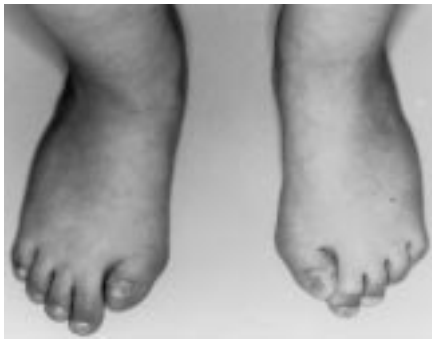


Fig. 1 Feet of a 3-year-old child with FOP. Note the symmetrical microdactyly of the great toes with valgus deviation at the metatarsophalangeal joints.

include baldness of the scalp, amenorrhea, and hearing impairment.[7]

Impending ossification at any site is heralded by painful nodules of highly vascular, noninflammatory fibroproliferative tissue involving tendons, ligaments, and the connective tissue of the skeleton.[13] These

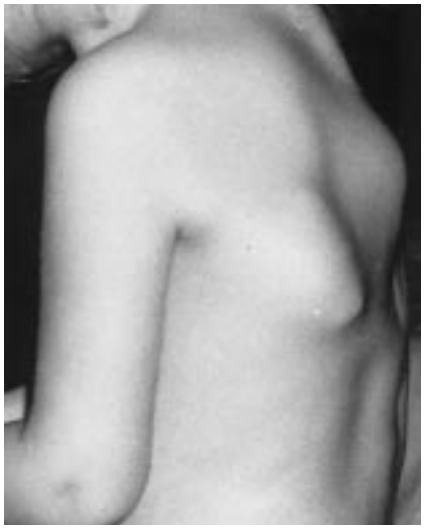


Fig. 2 Back of a 4-year-old girl with FOP. Note the characteristic subfasial nodules. (Reprinted with permission from Kaplan FS, Tabas JA, Gannon FH, et al: The histopathology of fibrodysplasia ossificans progressiva: An endochondral process. *J Bone Joint Surg Am* 1993;75:220-230.)

Large nodular soft-tissue swellings appear on the back and often prompt the suspicion of a connective tissue sarcoma (Fig. 2). If a putative diagnosis of FOP is not suspected on the basis of the malformation of the great toes, a lesional biopsy is often performed, which may lead to a misdiagnosis of aggressive juvenile fibromatosis, fibrosarcoma, chondrosarcoma, or extraosseous osteosarcoma, depending on the stage of maturation of the lesion.[13] New bouts of ectopic bone formation progress erratically throughout life and result in ankylosis of the major joints (Figs. 3 and 4). Most patients become completely immobilized and confined to a wheelchair or a permanent standing-sitting position by the third decade of life.

In a study of 44 patients,[14] ectopic ossification was noted to progress in several regular patterns. Ossification appears proximally before distally, axially before appendicularly, cranially before caudally, and dorsally before ventrally. The paraspinal muscles are involved early, with subsequent progression to the shoulder and hip regions (Fig. 5); the ankles, wrists, and jaw are commonly affected later. Other variable and unexplained clinical features

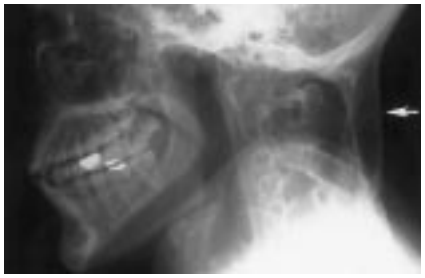


Fig. 3 Lateral radiograph of an adult patient with FOP shows ankylosed cervical vertebrae and a large bridge of heterotopic bone spanning the occiput to the upper back (arrow).

nodules rarely regress spontaneously, and most often mature rapidly through an endochondral sequence to form normal lamellar bone that rigidly immobilizes the joints of the axial and appendicular skeleton (Fig. 6). The mature heterotopic bone in FOP is indistinguishable histologically, radiographically, and biomechanically from mature skeletal bone.[13,15]

Bone formation can be triggered by blunt trauma but most often occurs spontaneously. Excision of heterotopic bone is futile, as surgical trauma predictably leads to the stimulation of new and more robust heterotopic ossification at the operative site.[7]

The diaphragm, extraocular muscles, heart, and smooth muscles are characteristically spared. Progressive spinal deformity is common in patients who have FOP (incidence of 65%). Scoliosis is most severe in patients who develop a unilateral pelvis–chest wall synostosis. Hypokyphosis results from early ossification of the paravertebral musculature.[16] Spinal bracing is ineffective, and surgical intervention is associated with numerous complications.[16] Untimely death often results from respiratory failure due to pneumonia or from inanition due to ankylosis of the jaw.[7,17]

The genetic mutation and pathogenesis of FOP are unknown. The lack of large families with this disorder precludes genetic linkage analysis; the exacerbation of the disease following surgical biopsy limits the availability of tissue for study; and the lack of a well-defined animal model limits in vivo systems suit-

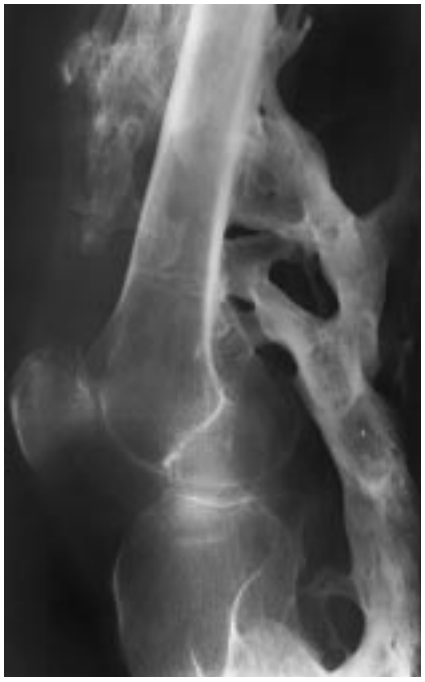


Fig. 4 Lateral radiograph of the knee of an adult patient with FOP shows extensive ossification bridging the femur and the tibia. (Reproduced with permission from Kaplan FS, Strear CM, Zasloff MA: Radiographic and scintigraphic features of modeling and remodeling in the heterotopic skeleton of patients who have fibrodysplasia ossificans progressiva. *Clin Orthop* 1994;304:238-247.)

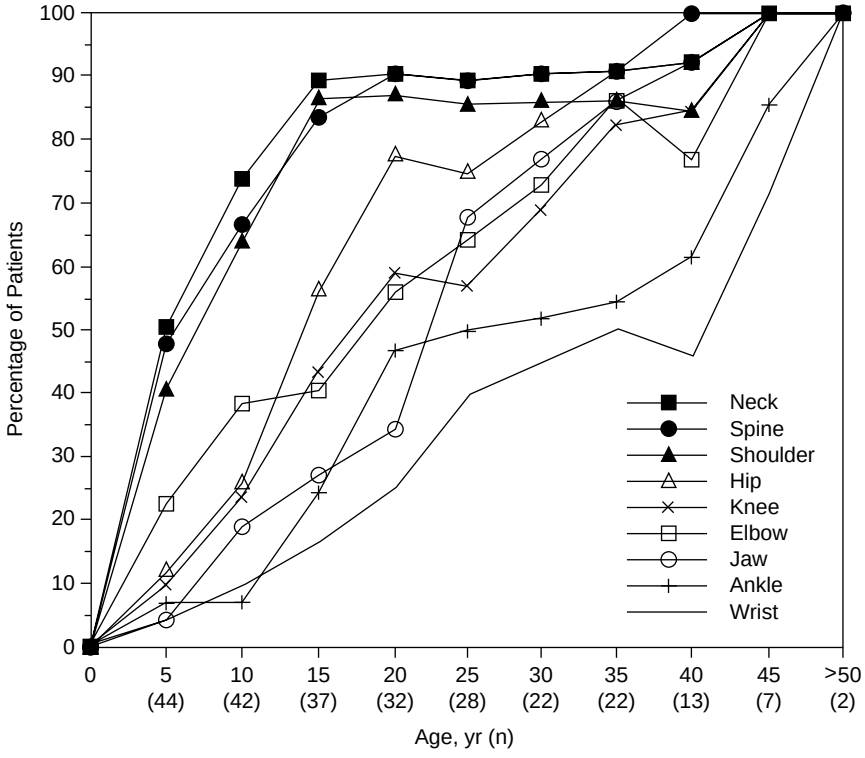
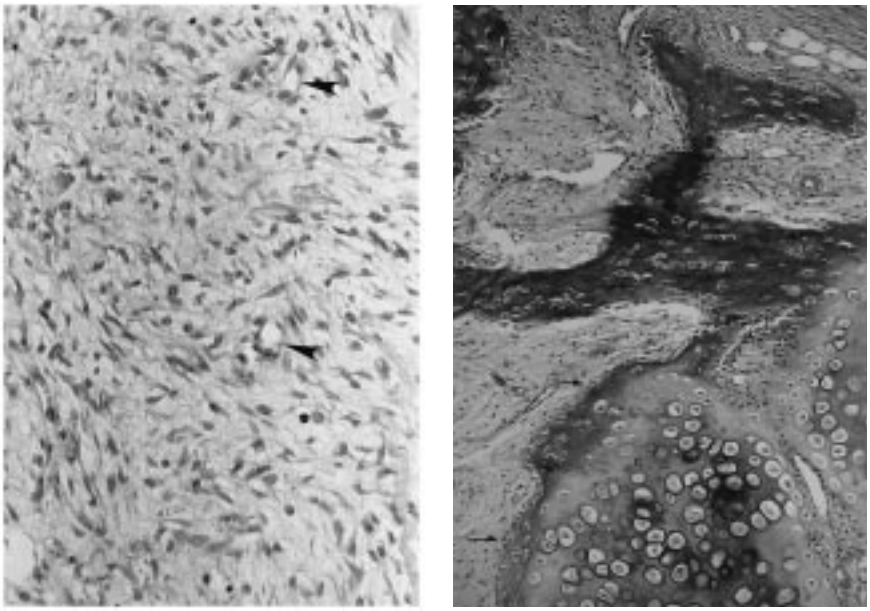


Fig. 5 Percentages of patients who had heterotopic ossification at each anatomic site, by age (value in parentheses below each age value represents number of patients who were in that age group at time of completion of survey). (Adapted with permission from Cohen RB, Hahn GV, Tabas JA, et al: The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva: A study of forty-four patients. *J Bone Joint Surg Am* 1993;75:215-219.)



A B

Fig. 6 **A,** Photomicrograph of an early FOP lesion shows loose fibroproliferative tissue with multiple small blood vessels (arrowheads) (hematoxylin-eosin; original magnification ×125). (Reproduced with permission from Kaplan FS, Tabas JA, Gannon FH, et al: The histopathology of fibrodysplasia ossificans progressiva: An endochondral process. *J Bone Joint Surg Am* 1993;75:220-230.) **B,** Photomicrograph of an intermediate FOP lesion shows endochondral osteogenesis. Arrows indicate osteoblasts; C = cartilage (hematoxylin-eosin, original magnification ×125).

able for experimentation. However, limited biologic material is available from careful venipuncture and emergency surgery, and the most logical experimental approach employs a candidate gene strategy.

The array of developmental gradients seen in FOP is similar to that seen in developmental anomalies induced by pleiotropic mutations of the decapentaplegic (*dpp*) locus in *Drosophila melanogaster*[18] (Table 3). It is intriguing that the protein encoded by *dpp* shares a 75% sequence homology with two BMPs (BMP2 and BMP4) and is the *Drosophila* homologue of BMP2 and BMP4. The recent demonstration that human BMP4 sequences can confer normal dorsalventral patterning in the *Drosophila* embryo suggests that the BMP gene family has the capacity to regulate pattern formation as well as tissue morphogenesis.[19] The BMPs are the only biomolecules discovered thus far that are capable of inducing endochondral ossification at a heterotopic site.[3] Since FOP is a disorder characterized by a disturbed developmental expression of the endochondral ossification program, it may represent a mutation resulting in a dominant gain of function.[20] The developmental expression of the BMP genes in mammals, the ability of recombinant BMP to induce heterotopic endochondral ossification,[2,3] and the developmental similarities between the decapentaplegic phenotype in the fly and the FOP phenotype in man[18,19] suggest a useful model for the study of FOP, with the BMPs as plausible candidate genes in genetic disorders of heterotopic ossification.

There is currently no effective treatment for FOP. Corticosteroids, diphosphonates, physical therapy, and surgical excision have all been tried in patients who have FOP, but without any objective benefit.[7,21] Patients who have FOP should be instructed assiduously to avoid precipitating factors such as blunt muscle trauma, intramuscular injections, injections of local anesthetics for dental procedures, and surgical attempts to excise ectopic bone.[7,13] A high index of suspicion should exist for common unrelated conditions such as appendicitis and cholecystitis. Surgical treatment of such conditions may be indicated.

Progressive Osseous Heteroplasia

Progressive osseous heteroplasia is another rare developmental disorder of heterotopic ossification, characterized by focal dermal ossification in infancy with progressive intramembranous ossification of subcutaneous fat and deep connective tissue[22] (Fig. 7). The disease presents as cutaneous

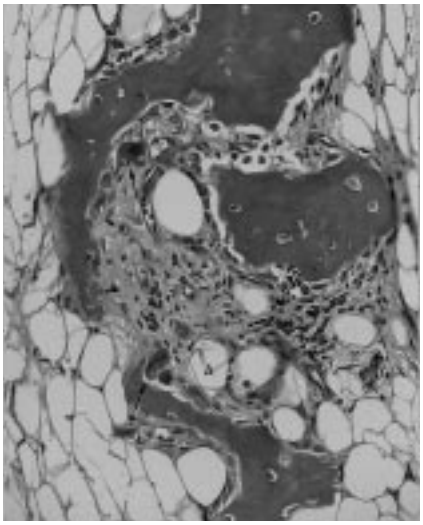


Fig. 7 Medium-power photomicrograph of subcutaneous tissue from the leg of a patient with POH. Note the irregular deposits of woven and lamellar bone surrounded by adipose tissue (A). Arrows indicate osteoclasts; arrowheads, osteoblasts (hematoxylin-eosin; original magnification ×200).

Table 3
Comparison of Developmental Gradients and Molecular Genetics in Two Recognized Phenotypes*

	Decapentaplegic	Fibrodysplasia Ossificans Progressiva
Affected species	*Drosophila melanogaster*	*Homo sapiens*
Affected genetic locus	*dpp*	?BMP
Protein product of locus	*dpp*	?BMP
Member of protein (peptide) superfamily	TGF-β	TGF-β
Closest homology in TGF-β superfamily	BMP	*dpp*
Developmental gradients†	1. Symmetrical defects in distal epidermal appendages	1. Symmetrical defects in distal limb blastema
	2. Dorsal-ventral embryonic determination	2. Dorsal-ventral gradient of heterotopic ossification
	3. Cranial (cephalic)-caudal subdivision of dorsal-ventral gradient	3. Cranial-caudal gradient of heterotopic ossification
	4. Axial-appendicular developmental gradient as seen in development of appendages from imaginal disks	4. Axial-appendicular gradient of heterotopic ossification
	5. Proximal-distal gradient of developmental defects in appendages	5. Proximal-distal gradient of heterotopic endochondral ossification

* TGF-β = type β transforming growth factor; ? = possibly.
† Revealed in *Drosophila melanogaster* by pleiotropic mutations in *dpp* gene and by embryonic patterns of *dpp* transcription. Revealed in *Homo sapiens* by natural history of disease.
(Adapted with permission from Kaplan FS, Tabas JA, Zasloff MA: Fibrodysplasia ossificans progressiva: A clue from the fly? *Calcif Tissue Int* 1990;47:117-125.)

plaques of ossification that coalesce and eventually progress to involve the adjacent connective tissues (Fig. 8). This extensive ossification of the deep tissues often results in ankylosis of affected joints and focal growth retardation of involved limbs. The etiology and pathogenesis of the disorder are unknown.

The anatomic distribution of lesions in POH suggests that the pathogenesis may involve a mesenchymal stem cell destined for widespread mosaic distribution. Although dermal fibroblasts and internal limb structures arise embryonically from limb-bud mesenchyme, the fate map of the blastoderm mammalian embryo suggests that muscle and bone cell types are of polyclonal origin. Conversely, in the mature organism, a single cell, such as a hematopoietic stem cell or a mesenchymal stem cell, can generate a wide variety of cell types. At present, little is known about the molecular mechanisms of the signal and response system of mesodermal induction, and the clonal nature of lesions in POH remains a mystery.[22]

The heterotopic ossification in POH occurs predominantly by an intramembranous pathway, and is similar to that observed in Albright's hereditary osteodystrophy. The lesions in the latter condition are limited to the skin, while those in POH also involve the deeper tissues. Furthermore, no patient with POH has had the morphologic or endocrine disturbances characteristically seen with Albright's hereditary osteodystrophy. The heterotopic ossification in POH appears to be the only manifestation of the disease. The patients thus far all have normal intelligence, normal developmental milestones, and no biochemical or endocrine abnormalities, except for transient elevations in serum alkaline phosphatase concentration.[22]

The long-term prognosis for patients who have POH is uncertain, as only one of the six cases has been followed up beyond adolescence. At present, there is no definitive prevention or treatment available for children with POH. The extensive coalescence of ossified skin plaques and the relentless progressive ossification of deep tissues pose perplexing therapeutic dilemmas.[22]

Experimental Models

The earliest experimental models of heterotopic ossification involved

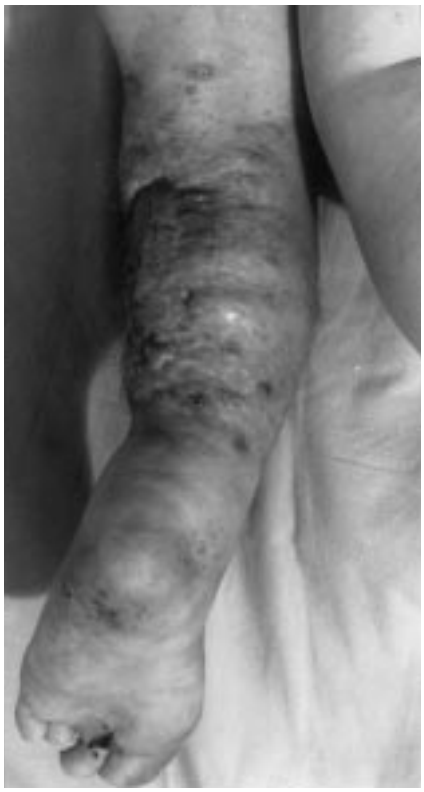


Fig. 8 Posterior aspect of the left leg and popliteal fossa of a patient with POH. Note extensive maculopapular lesions.

blunt trauma to tendon and muscle tissue, forced joint manipulation following prolonged immobilization, and intramuscular injection of chemical irritants, such as calcium chloride, ethanol, and quinine. Later experiments illustrated the osteogenic potential of different cell types. In the classic experiments of Huggins, heterotopic bone formation was induced by autotransplantation of bladder transitional epithelium into the rectus abdominis sheath of dogs. The bone formed in these experiments developed directly from the mesenchymal tissue without cartilage precursors. Huggins' experiments revealed the importance of a conducive environment, as bone was not formed when the epithelium was transplanted into liver, kidney, or spleen. Grafts of skeletal tissue, such as whole bone, cartilage, and bone marrow, have also induced heterotopic ossification.

Urist demonstrated that demineralized bone matrix induced bone formation when injected intramuscularly or subcutaneously into rodents or rabbits. Urist termed this osteoinductive factor "bone morphogenetic protein."[23] Following implantation, bone matrix stimulates migration of mesenchymal stem cells, which subsequently differentiate into cartilage- and bone-forming cells. Within 1 week, cartilage forms and calcification of the cartilage begins. Ossification and the development of bone marrow result in a fully functioning ossicle of mature heterotopic bone.[6]

While the osteoinductive properties of BMP were clearly reproducible, the precise composition of proteins remained elusive until recently. In pioneering work, Wozney and colleagues isolated and characterized seven unique BMPs.[2,3] The protein-coding regions for these seven polypeptides have been cloned and termed BMPs 1 through 7. On the basis of their amino acid sequence homology and conservation of cysteine residues, BMPs 2 through 7 are closely related members of the transforming growth factor superfamily.[2,3] Furthermore, BMPs 2 through 7 all exhibit chondrogenic and osteogenic properties in a rat ectopic bone assay system.[2,3]

In a unique rat model, Khouri et al[24] demonstrated that muscle flaps that received injections of recombinant BMP3 and were then coated with demineralized bone matrix and placed in molds could be transformed into mature cancellous bone that matched the exact shape of the molds. Further analysis of the molecular organization and regulation of the BMP genes will enhance our understanding of their role in normal and heterotopic bone induction.

Physical Features and Laboratory Findings

The symptoms, signs, and laboratory findings are similar in most forms of heterotopic ossification, permitting a generic description. Heterotopic ossification, regardless of the cause, is associated with local symptoms of pain, swelling, and decreased mobility of adjacent joints (Table 4). The early lesions often appear inflammatory and may be mistaken for cellulitis, infection, thrombophlebitis, tumor, or soft-tissue amorphous nonosseous calcification. A detailed medical history will reveal distinguishing clues that help in confirming or excluding disorders unrelated to heterotopic ossification.

Serum calcium and phosphorus levels are normal in all forms of heterotopic ossification and will exclude metastatic calcification. The serum alkaline phosphatase concentration will be elevated early in the course of heterotopic ossification but will return to normal as maturation proceeds. Radionuclide bone scans are sensitive but nonspecific and show dramatic increased uptake early in the course of heterotopic ossification before mineralization is apparent on plain radiographs. Biopsy may be helpful in excluding an ossifying soft-tissue tumor. However, biopsy often exacerbates heterotopic ossification, especially in patients who have FOP.

Treatment

Numerous pharmacologic and physical modalities, such as diphosphonates, nonsteroidal anti-inflammatory drugs (NSAIDs), radiation therapy, physical therapy, and surgical resection, have been used in the treatment of heterotopic ossification (Fig. 9). These modalities have proved useful in the prevention of various forms of heterotopic ossifi-

Table 4
Clinical and Laboratory Manifestations of Heterotopic Ossification

	Early (0–4 wk)	Intermediate (5–15 wk)	Late (16–25 wk)
Symptoms	Increased pain, swelling, and stiffness	Pain, swelling, and stiffness	Decreased pain, swelling, and stiffness
Signs*	Erythema, warmth, induration, tenderness, decreasing ROM	Further decreasing ROM	Decreased ROM, possible ankylosis
Serum alkaline phosphatase level	Elevated	Elevated, then plateaus	Returns to normal
Histopathologic findings	Mesenchymal metaplasia	Osseous or chondro-osseous differentiation	Bone
Radionuclide bone scan	Positive phases I and II	Positive phase III	Decreasing phase III
Radiographic findings	None or soft-tissue swelling	Early osteogenesis	Late osteogenesis with remodeling

* ROM = range of motion.
(Adapted with permission from Brighton C [ed]: *Bone Formation and Regeneration*. Rosemont, Ill: American Academy of Orthopaedic Surgeons [in press].)

cation, but at present there are no generally accepted preventive measures against heterotopic ossification.[25]

For many years, etidronate enjoyed great popularity in the prevention of heterotopic ossification. However, recent data indicate that brief courses of diphosphonates, such as etidronate, merely delay the mineralization of osteoid matrix, and are ineffective in the long-term inhibition of clinically significant heterotopic ossification.

Various nonsteroidal anti-inflammatory medications have been used successfully in preventing some forms of heterotopic ossification, especially following total hip arthroplasty. The nonsteroidal anti-inflammatory medications act by inhibiting synthesis of prostaglandins, which are possible mediators of heterotopic ossification.

Radiation therapy has been used widely since 1981 in the prevention of recurrent heterotopic ossification in high-risk patients who have an acquired form of the disorder and who have undergone resection of a mature lesion. Coventry and Scanlon recommended ten 2,000-rad doses within 10 days to 2 weeks following resection of a mature heterotopic ossified lesion. However, new protocols recommend lower doses of 700 to 800 rad within 1 to 4 days postoperatively and for no more than two doses. These lower doses, directed to the site of ossification within several days of surgical excision, appear to be as effective as the higher-dose, longer-duration regimens. The theoretical target of radiation therapy is the localized pool of inducible osteoprogenitor cells.[25]

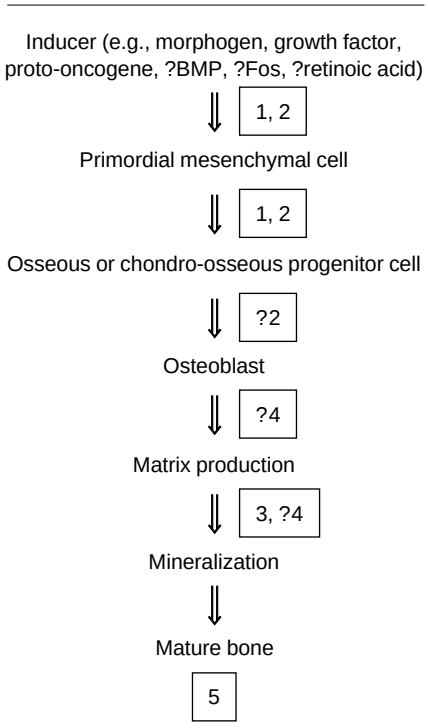


Fig. 9 Effect of various types of therapy on mechanistic pathway of heterotopic ossification (1 = radiation; 2 = NSAIDs; 3 = etidronate; 4 = physical therapy; 5 = surgical excision). (Adapted with permission from Brighton C [ed]: *Bone Formation and Regeneration.* Rosemont, Ill: American Academy of Orthopaedic Surgeons [in press].)

Physical therapy has remained controversial as a prevention and treatment modality for heterotopic ossification. Aggressive stretching of spastic limbs has been implicated as a causative factor in heterotopic ossification. Other reports have shown that gentle passive range-of-motion exercises may be beneficial in inhibiting heterotopic ossification of neurogenic origin. Neither the beneficial nor the adverse effects of physical therapy are understood.

Surgical excision of heterotopic bone should be limited to patients who have advanced symptoms or

ankylosis, and must be delayed until the heterotopic bone is mature, as determined by radiographic and radionuclide studies. The cause of the heterotopic ossification may be the most important factor when considering surgical management. While surgical resection may be beneficial in some cases, it is ineffective or detrimental in others. In FOP, operative removal of mature heterotopic bone is contraindicated because surgery invariably results in recurrence of ossification and may cause extensive progression of the disease.

Summary

In this brief review, we have discussed some of the more common causes of heterotopic ossification seen in orthopaedic practice, but we have focused on two rare genetic and developmental disorders of heterotopic ossification, FOP and POH, that have the potential to illuminate common pathways of the induction of heterotopic bone.

Insight gained from the study of rare disorders of heterotopic ossification will enhance our understanding of the normal pathways of bone formation. As William Harvey, the discoverer of the circulatory system, wrote in 1657:

> Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by careful investigation of cases of rarer forms of disease. For it has been found in almost all things, that what they contain of useful or applicable [nature] is hardly perceived unless we are deprived of them, or they become deranged in some way.[26]

References

1. Chalmers J, Gray DH, Rush J: Observations on the induction of bone in soft tissues. *J Bone Joint Surg Br* 1975;57:36-45.
2. Wozney JM, Rosen V, Celeste AJ, et al: Novel regulators of bone formation: Molecular clones and activities. *Science* 1988;242:1528-1534.
3. Wozney JM, Rosen V, Byrne M, et al: Growth factors influencing bone development. *J Cell Sci Suppl* 1990;13:149-156.
4. Caplan AI: Mesenchymal stem cells. *J Orthop Res* 1991;9:641-650.
5. Boström K, Watson KE, Horn S, et al: Bone morphogenetic protein expression in human atherosclerotic lesions. *J Clin Invest* 1993;91:1800-1809.
6. Puzas JE, Miller MD, Rosier RN: Pathologic bone formation. *Clin Orthop* 1989;245:269-281.
7. Connor JM, Evans DAP: Fibrodysplasia ossificans progressiva: The clinical features and natural history of 34 patients. *J Bone Joint Surg Br* 1982;64:76-83.
8. Connor JM, Evans DAP: Genetic aspects of fibrodysplasia ossificans progressiva. *J Med Genet* 1982;19:35-39.
9. Kaplan FS, McCluskey W, Hahn G, et al: Genetic transmission of fibrodysplasia ossificans progressiva: Report of a family. *J Bone Joint Surg Am* 1993;75:1214-1220.
10. Schroeder HW Jr, Zasloff M: The hand and foot malformations in fibrodysplasia ossificans progressiva. *Johns Hopkins Med J* 1980;147:73-78.
11. Cremin B, Connor JM, Beighton P: The radiological spectrum of fibrodysplasia ossificans progressiva. *Clin Radiol* 1982;33:499-508.
12. Thickman D, Bonakdar-pour A, Clancy M, et al: Fibrodysplasia ossificans progressiva. *AJR* 1982;139:935-941.
13. Kaplan FS, Tabas JA, Gannon FH, et al: The histopathology of fibrodysplasia ossificans progressiva: An endochondral process. *J Bone Joint Surg Am* 1993;75:220-230.
14. Cohen RB, Hahn GV, Tabas JA, et al: The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva: A study of forty-four patients. *J Bone Joint Surg Am* 1993;75:215-219.
15. Kaplan FS, Strear CM, Zasloff MA: Radiographic and scintigraphic features of modeling and remodeling in the heterotopic skeleton of patients who have fibrodysplasia ossificans progressiva. *Clin Orthop* 1994;304:238-247.
16. Shah PB, Kaplan FS, Drummond D, et al: The natural history of spinal deformity in patients who have fibrodysplasia ossificans progressiva. *J Bone Mineral Res* 1993;8(suppl 1):S403.
17. Connor JM, Evans CC, Evans DAP: Cardiopulmonary function in fibrodysplasia ossificans progressiva. *Thorax* 1981;36:419-423.
18. Kaplan FS, Tabas JA, Zasloff MA: Fibrodysplasia ossificans progressiva: A clue from the fly? *Calcif Tissue Int* 1990;47:117-125.
19. Padgett RW, Wozney JM, Gelbart WM: Human BMP sequences can confer normal dorsal-ventral patterning in the *Drosophila* embryo. *Proc Natl Acad Sci U S A* 1993;90:2905-2909.
20. Jones CM, Lyons KM, Hogan BLM: Involvement of bone morphogenetic protein-4 (BMP-4) and Vgr-1 in morphogenesis and neurogenesis in the mouse. *Development* 1991;111:531-542.
21. Rogers JG, Geho WB: Fibrodysplasia ossificans progressiva: A survey of forty-two cases. *J Bone Joint Surg Am* 1979;61:909-914.
22. Kaplan FS, Craver R, MacEwen GD, et al: Progressive osseous heteroplasia: A distinct developmental disorder of heterotopic ossification. *J Bone Joint Surg Am* 1994;76:425-436.
23. Urist MR: Bone: Formation by autoinduction. *Science* 1965;150:893-899.
24. Khouri RK, Koudsi B, Reddi H: Tissue transformation into bone in vivo: A potential practical application. *JAMA* 1991;266:1953-1955.
25. Pellegrini VD Jr, Konski AA, Gastel JA, et al: Prevention of heterotopic ossification with irradiation after total hip arthroplasty: Radiation therapy with a single dose of eight hundred centigray administered to a limited field. *J Bone Joint Surg Am* 1992;74:186-200.
26. Garrod A: The lessons of rare maladies. *Lancet* 1928;1:1055-1060.