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CRITICAL REVIEW

HETEROTOPIC OSSIFICATION: PATHOPHYSIOLOGY, CLINICAL FEATURES, AND THE ROLE OF RADIOTHERAPY FOR PROPHYLAXIS

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Heterotopic ossification (HO) is a benign condition of abnormal formation of bone in soft tissue. HO is frequently asymptomatic, though when it is more severe it typically manifests as decreased range of motion at a nearby joint. HO has been recognized to occur in three distinct contexts—trauma, neurologic injury, and genetic abnormalities. The etiology of HO is incompletely understood. A posited theory is that HO results from the presence of osteoprogenitor cells pathologically induced by an imbalance in local or systemic factors. Individuals at high risk for HO development frequently undergo prophylaxis to prevent HO formation. The two most commonly employed modalities for prophylaxis are nonsteroidal anti-inflammatory drugs and radiation therapy. This review discusses HO pathophysiology, clinical features, and the role of radiotherapy for prophylaxis. © 2006 Elsevier Inc.

Heterotopic ossification, Heterotopic bone, Radiation therapy, Prophylaxis.

INTRODUCTION

Heterotopic ossification (HO) is defined as the abnormal formation of mature, lamellar bone in soft tissues, often containing bone marrow. Heterotopic ossification was first identified in 1883 by Riedel, a German physician. It was later described as "paraosteoarthropathy" by French physicians Dejerne and Ceillier based on observations of patients with traumatic paraplegia in World War I (1). HO has been given multiple names including paraosteoarthropathy, myositis ossificans, periarticular new bone formation, periarticular ectopic ossification, neurogenic osteoma, neurogenic ossifying fibromyopathy, and heterotopic calcification (2). HO is the more accurate descriptor.

Soft-tissue calcifications can be divided into two categories—dystrophic and metastatic. Dystrophic calcification is calcium deposition that occurs in the setting of soft-tissue insult. HO is one etiology of dystrophic soft-tissue calcification, though it can be distinguished histologically from other forms of dystrophic calcification by the presence of a trabecular pattern characteristic of bone. Metastatic calcification is characterized by the development of diffuse pathologic calcification resulting from an elevated calcium-phosphate product as seen in renal failure and hyperparathyroidism.

There are three recognized etiologies of HO: traumatic, neurogenic, and genetic. Traumatic HO typically follows fractures, dislocations, operative procedures, and severe burns. Most commonly, HO is seen around the hip after fracture and open reduction-internal fixation (ORIF) procedures or total hip arthroplasties (THA) (Fig. 1). HO of the hip often involves the abductor compartment, though any compartment surrounding the hip can be involved (3). Burns from either thermal or electrical injury can precipitate HO, with the most frequently involved joint being the elbow (Fig. 2a), though any major joint can be affected (4). Other reported sites of joint HO after trauma include the knee (5) (Fig. 2b), shoulder (6), ankle (7), and temporomandibular joint (8). HO has also been reported in soft-tissue locations not surrounding joints in the setting of trauma, including the quadriceps muscles after contusion (9) and abdominal wounds after surgery (10).

Neurogenic HO is seen after central nervous system insult, including spinal trauma and head injuries. The most commonly involved joint is the hip followed by the shoulder and elbow (11). Other neurologic conditions have also been implicated in the development of HO, including encephalitis (12), meningitis (13), myelitis (14), tetanus (15), brain tumors (16), epidural abscess (17), and subarachnoid hemorrhage (18).

Finally, HO can occur in the setting of genetic disorders, including fibrodysplasia ossificans progressiva (FOP), progressive osseous heteroplasia (POH), and Albright's hereditary osteodystrophy (AHO). FOP is a rare, autosomal dominant genetic disorder associated with progressive, disabling HO. HO begins in childhood and can be spontaneous or trauma-induced. By early adulthood, progressive ossifica-

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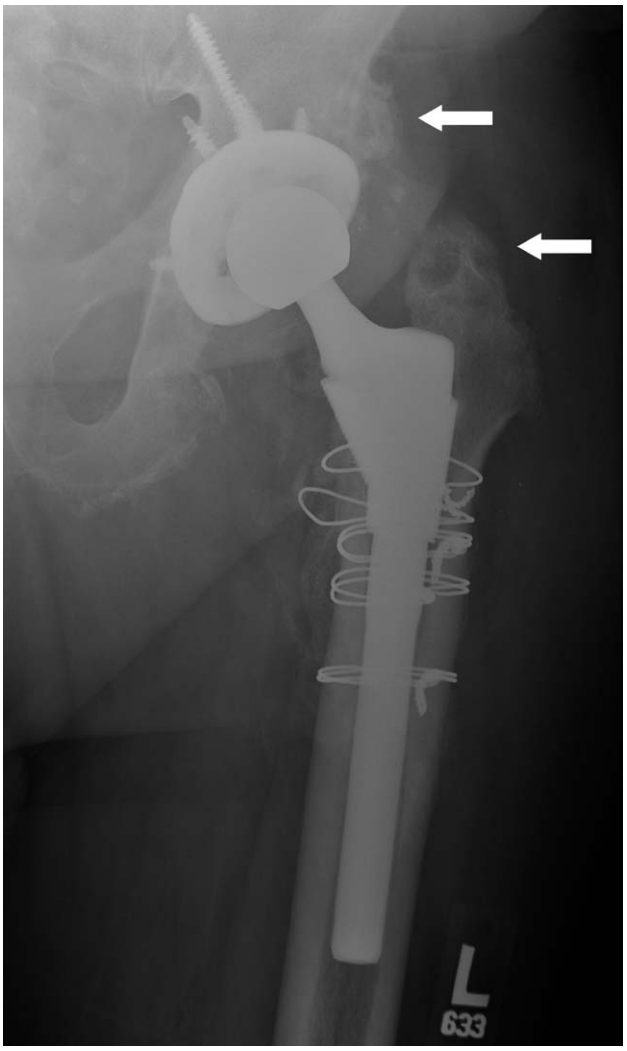

Fig. 1. Heterotopic ossification (arrows) following total hip arthroplasty.

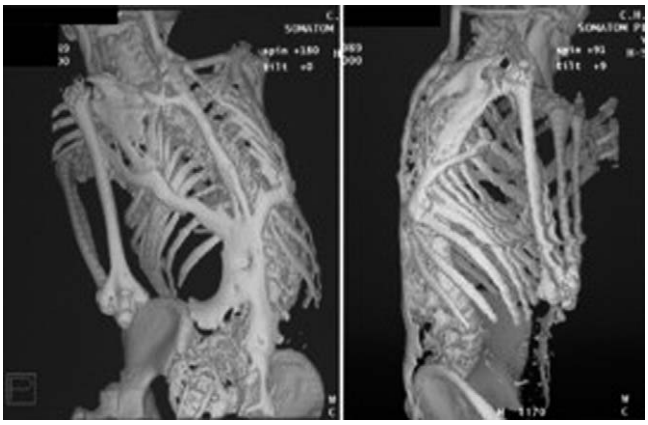

Fig. 3. Reconstructed computed tomography scan of a 12-year-old child with fibrodysplasia ossificans progressiva. Reprinted from Glaser DL, Economides AN, Wang L, *et al.* In vivo somatic cell gene transfer of an engineered Noggin mutein prevents BMP-4–induced heterotopic ossification. *J Bone Joint Surg* 2003;85-A: 2332. Reproduced with permission of the *Journal of Bone and Joint Surgery*.

tion leads to ankylosis of all major joints of the axial and appendicular skeleton, eventually eliminating joint motion (Fig. 3) (19). POH is a rare genetic condition causing extensive dermal HO in infancy that progresses to HO of the deeper tissues. AHO is a complex disorder involving developmental defects often coupled with resistance to parathyroid hormone. AHO can also involve dermal and subcutaneous HO. POH and AHO are believed to be related conditions stemming from mutations of the *GNAS1* gene, resulting in decreased expression or dysfunction of the alpha subunit of the stimulatory G protein of adenylyl cyclase (20).

Clinical presentation

Heterotopic ossification is typically asymptomatic and detected only as an incidental finding on a radiograph.

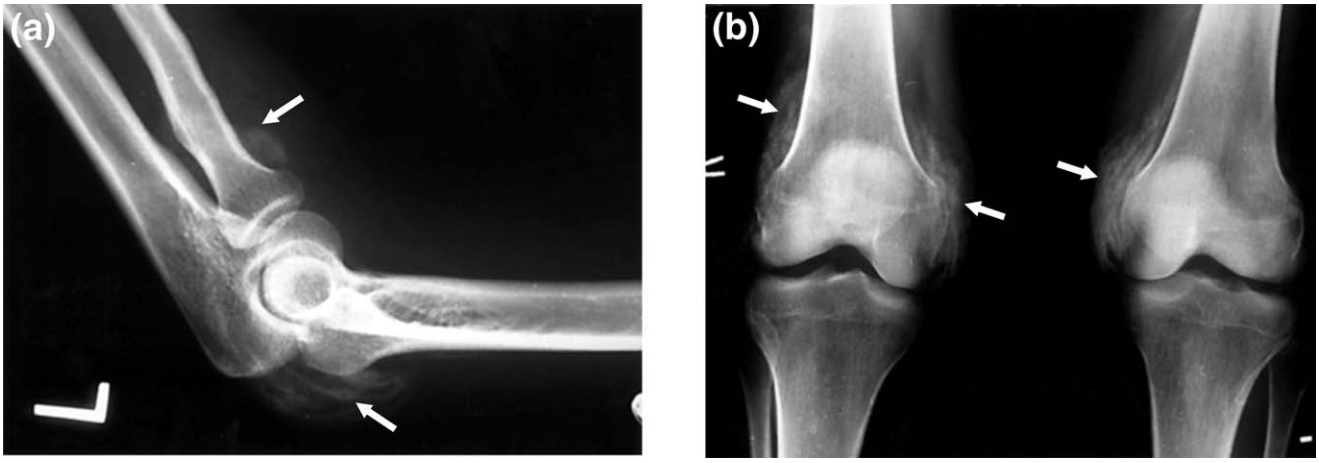

Fig. 2. (a) Heterotopic ossification (arrows) of the elbow. Reprinted from Lane JE, Dean RJ, Foulkes GD, *et al.* Idiopathic heterotopic ossification in the intensive care setting. *Postgrad Med J* 2002;78:494. Reproduced with permission of the British Medical Journal Publishing Group. (b) Heterotopic ossification (arrows) of the knee. Reprinted from Lane JE, Dean RJ, Foulkes GD, *et al.* Idiopathic heterotopic ossification in the intensive care setting. *Postgrad Med J* 2002;78:495. Reproduced with permission of the British Medical Journal Publishing Group.