INTRODUCTION

Chronic painful foot and ankle conditions can be challenging diagnostic dilemmas that are frustrating to both patients and treating podiatric physicians alike. Identification of a specific etiology for the pain greatly aids both nonoperative and operative treatment strategies. A multitude of possible reasons, either local or systemic at various tissue levels, may be responsible for the clinical symptom of foot and ankle pain. Bone marrow abnormalities should not be overlooked as a possible etiology for chronic painful foot and ankle conditions whether traumatic or nontraumatic in origin. Bone marrow abnormalities are becoming more recognized as an etiology of foot and ankle pain. Understanding their pathophysiology, as is best known today, is important to considering their possibility in clinical practice. Once recognized and appropriately managed, response to treatment with subsequent relief of pain can be very rewarding. A discussion of bone marrow abnormalities is presented with an illustrative clinical case of persistent foot pain that responded well to treatment following appropriate recognition and diagnosis.

CLINICAL CASE PRESENTATION

A 60-year-old female in good health, other than osteoporosis and a history of Raynaud’s disease, presented with a concern of pain in the lateral column area of the left foot of three months duration. There was an abrupt onset of pain after a mild traumatic incident consisting of a miss-step in an inversion direction while wearing shoes. Clinical and radiographic evaluation two months after the injury was essentially unremarkable (Figure 1). Her working diagnosis was a mild midfoot sprain. Over the next month her pain did not improve with treatment including moderation of activity, supportive shoes including foot orthoses, and anti-inflammatory medication. The pain was of a significant degree limiting daily activities. It was described as a deep achy soreness with activity relieved with rest, improved with shoes and foot orthoses. It was basically unimproved and unchanged since the onset 3 months prior even with treatment over the previous month.

Clinical evaluation at three months following pain onset showed a satisfactory neurovascular status with no gross malalignment or deformity to the affected foot. There was bilateral symmetry to her feet in terms of structural position, function, and ranges of motion. There was a degree of edema without erythema or callus over the lateral left midfoot area. Fairly acute pain was noted at palpation of the fifth metatarsocuboid joint as well as to the body of the cuboid itself. The subjective pain was not in the area of palpation, but described as feeling deeper within the foot. Soft tissues were intact and without compromise or pain, in particular to palpation and function of the peroneal tendons. She demonstrated a propulsive gait without a substantial limp. Foot radiographs compared to the study of one month prior were essentially unremarkable and unchanged with a degree of osteoporosis and mild diffuse arthritic changes to the midfoot joints. There was no evidence of bone callus, fracture, or joint malalignment (Figure 2).

There was concern not only with the degree and persistence of pain that was unresponsive to treatment with few clinical or radiographic findings, but a discrepancy between the objective and subjective location of her pain. A three-phase Technetium bone scan was ordered to help identify a possible inflammatory nidus for her pain that might help direct more specific review of bone and soft tissues with a magnetic resonance image (MRI) study (Figure 3). The presumptive diagnoses included midfoot sprain, midfoot osteoarthritis, and a possible delayed union of a fracture or stress fracture of the cuboid. Her treatment approach was modified to include elastic ankle bracing, continuing supportive shoes with foot orthoses and activity moderation to tolerance. The delayed images of the bone scan showed mildly increased activity near the fourth metatarsal base of the affected foot. There were no other significant findings noted. An MRI of the area of concern demonstrated subtle bone marrow edema in the cuboid and
Figure 1A. Anterior-posterior radiograph at initial presentation 2 months following onset of symptoms.

Figure 1B. Oblique radiograph.

Figure 1C. Lateral view.

Figure 2A. Anterior-posterior radiograph at 3 months following onset of symptoms, 1 month after initiating treatment.

Figure 2B. Oblique view.

Figure 2C. Lateral view.
lateral cuneiform consistent with stress injury. No other
evidence of osseous or soft tissue injury as well as no
anatomical abnormalities was found (Figure 4).

Her diagnosis following testing was painful traumatic
bone marrow edema or bone bruise of the left cuboid and
lateral cuneiform with an early delay in union or healing. At
the time, a stress fracture of the cuboid was considered, but
on retrospect was probably not likely. Only a portion of the
cuboid itself showed changes on the MRI. Several adjacent
bones were noted with similar MRI changes, which is more
typical of stress or injury to the bone without frank fracture.
The pattern of the MRI changes was not linear, but more
diffuse. In time there were no radiographic changes typical
of cuboid stress fracture healing.

Treatment was instituted including daily use of a
removable immobilizing walking boot combined with an
Exogen 4000+ Ultrasound Bone Healing System (Smith &
Nephew) bone stimulator at 20 minutes application daily.
After 1 month there was notable improvement in pain with
continued improvement through the second month with
pain levels reduced to only a mild soreness. By three months
into treatment there was near complete resolution of pain
and the immobilizing boot was discontinued and the bone
stimulator continued for an additional three months for a
total of six months use. Periodic serial radiographs showed
no new findings or changes in the bone or soft tissues of the
foot. She had become completely asymptomatic by six
months following initiation of treatment and there was a full
return to daily activities and exercise without recurrence of
pain. At one year following treatment, foot radiographs
remained unchanged (Figure 5). A follow-up comparison
MRI showed absence of the bone marrow edema findings
noted on the previous study (Figure 6).
Figure 4C. T1-weighted image at 3 months.

Figure 4D. T1-weighted image, lateral view.

Figure 5A. Anterior-posterior radiograph at 1 year following treatment with complete resolution of symptoms.

Figure 5B. Oblique view.

Figure 5C. Lateral view.
DISCUSSION

Bone marrow abnormalities or bone edema can be difficult to appreciate, not only because it is not well understood, but because the literature is somewhat inconsistent and based on both fact and theory. Bone marrow abnormalities were only discovered with the advent of MRI to assess more occult injuries because bone marrow abnormalities are not evidenced on radiographs. They are clinically relevant, important to appreciate as a source of real and potentially treatable short or long term foot and ankle pain. Bone marrow edema or bone marrow abnormalities are described as ill-defined areas of low signal intensity on T1-weighted MRI images and intermediate to high signal intensity on T2-weighted MRI images (1). Various ankle and pedal bones with varying amounts of involvement in varying locations within the bones have been described. The talus is by far the most frequent followed by the navicular, medial malleolus, and cuboid. They may be asymptomatic or present with pain. They can be present for many months especially if nontraumatic in origin such as in avascular necrosis (AVN) or shorter in duration if more bone stress-related and associated with fractures. (1) Their incidence is basically unknown and interestingly, bone marrow abnormalities are described in the literature as both rare and common. They may present in defined conditions where treatment is understood and prognosis is predictable such as diabetic neuroarthropathy (2), osteomyelitis (2), tendon abnormalities (3-5), neoplasm, bone contusion, and stress fracture (6). Likewise, the etiology may be less clearly understood and related to possible altered mechanics (7), stress reaction (8), or early osteonecrosis (8), where the outcome regardless of treatment is more unpredictable. As a rule traumatic type etiologies tend to respond well to treatment over a shorter period of time than nontraumatic etiologies. (1) The etiology of bone marrow abnormalities or bone marrow edema may remain unknown. Bone marrow edema is seen coincidentally and more frequently in patients...
with osteoporosis (9) and low systemic bone mineral density or following a period of foot and leg immobilization (10). No bone marrow changes were found in MRI evaluations in patients with reflex sympathetic dystrophy (11).

There is controversy concerning the pathophysiology of bone marrow edema. Bone marrow edema has been described as possibly a distinct self-limiting clinical entity, a kind of reflex sympathetic dystrophy, or a diffuse but reversible early phase of AVN. Histological samples from the hip, knee, and ankle are reported to show a picture of marrow edema without fat necrosis with active osteoblasts along thin seams of woven bone in the marrow. In the cancellous bone there is thinning of the trabeculae and osteoclastic bone resorption suggesting the condition is unrelated to AVN (12). Fat necrosis has been observed in other reports that resolved with satisfactory healing suggesting an early reversible stage of AVN produced by modest ischemia (13). The cartilage overlying bone bruises has been shown to demonstrate both histological changes of chondrocyte and matrix degeneration combined with biochemical changes (14). The true pathophysiology remains unclear (15).

Specific diagnosis of painful bone marrow edema is typically by exclusion. History and physical findings may help identify local or systemic etiologies. Radiographs of bone marrow abnormalities such as bone bruises show radiolucencies in larger bones, but are far less specific, if seen at all, in the foot and ankle. Radiographs are more helpful in ruling out other etiologies for pain than ruling in a diagnosis of bone marrow edema of the foot and ankle. Computerized axial tomography (CAT) scans may show osteopenia, but are insensitive to bone marrow edema. MRI is the only imaging modality that permits direct detection of bone marrow edema (9). Three types of bone marrow edema patterns on MRI have been described. The first is an ill-defined edema-like zone, the second is an edema-like zone with well-defined necrosis-like zones, and the third is an edema-like zone plus linear structures. More than one type could be seen in the same patient. Patients with the necrosis zone were noted to remain symptomatic longer and respond more poorly to treatment regardless of etiology than the other types. The ill-defined edema-like zone is typical of a bone bruise. The presence of a necrosis zone is more typical of AVN, but not always found. The presence of linear structures is more typical of subtle stress fractures (1).

Several specific conditions of bone marrow edema have been described. A bone bruise or trabecular microfracture is considered as the presence of bone marrow edema associated with trauma or abnormal biomechanical forces. They may occur as a result of ankle instability long-term following ligamentous injury or as a result of microavulsion and impaction at the time of injury. Their presence has been noted in 39% of ankle sprains, 35% in lateral ankle injuries, and 69% in medial deltoid injuries. (16) The presence of bone marrow edema on ankle MRI implies either ankle ligamentous instability long term or ligamentous injury short term. Transient bone marrow edema has been described as an uncommon, atraumatic and painful type of bone marrow edema linked to osteoporosis. The etiology is unknown as it is a diagnosis of exclusion. This painful condition generally responds well to immobilization management. Avascular necrosis begins with a bone marrow edema phase combined with necrosis that unlike bone marrow edema conditions alone is progressive and typically results in time with bone and joint collapse.

The case presented more than likely demonstrates a painful bone bruise in a patient with osteoporosis associated with a subtle injury. A bone fracture time-line can be appreciated from unloaded resting bone progressing to an occult fracture. In the fracture time-line resting bone with applied stress undergoes normal loading that can progress to a point where no real injury or fracture has occurred and there is no pathological response. Further force application can result in the bone being stressed substantially, but not damaged and the living bone tissue reacts to that stress. The bone marrow can show edema on MRI in the absence of any radiographic findings. Further load can lead to trabecular disruption or micro-fraction damage to the bone structure, but still no fracture or fracture healing that would be evident radiographically only the development of bone marrow edema seen on MRI. The bone injury defined as a bone bruise may only be appreciated microscopically on biopsy or on MRI as bone marrow edema. The bone injury to this point in a sensate individual could be rather painful. Likewise, it may be possible that healing of the bone bruise may not progress and a state of nonunion, or possibly more appropriately stated non-healing occurs as there is no occult fracture. In this non-healing bone bruise state the associated persistence of pain could respond to fracture management. Bone bruises are typically expected to heal and resolve by 3-4 months (14). Further injury force application to the bone beyond the bone bruise level can result in the typical clinical and radiographic findings of a fracture.

The fracture eventually progresses over time to demonstrate the predictable radiographic changes of the stages of fracture healing. The varied levels of stress forces on the multiple small bones of the foot and ankle in any single traumatic situation can result in a myriad of combinations of bone injury extending from bone bruises with bone marrow edema only appreciated on MRI to the occult fractures seen on radiographs, not to mention associated soft tissue injuries. The possibility of these
combination injuries makes sense and any one or more of the injuries may result in a persistence of pain long term if failure of bone healing of any of them occurs. The significant degree of persistent pain in the particular case reviewed here may have been a result of slowness of the bone bruise to resolve itself through the bone healing process even after healing of the soft tissue component of the injury. The pain improved with fracture management.

Pain relief with bone bruise healing typically is completed by 3-4 months. A time-line similar to bone injury could be considered in non-traumatic bone marrow edema possibilities other than bone bruises such as stress reaction, biomechanical stress, ligamentous instability, tendon abnormalities, and stress fractures. Interestingly, foot and ankle tendon pathology such as enthesopathy or tendonitis can result in bone marrow changes as secondary reactions with MRI evidence within the adjacent bone structures (17). These bone marrow abnormalities themselves as well as the tendonitis or enthesopathy could all account for the pain experienced clinically as well as any lack of response to treatment. A greater incidence of symptomatic bone marrow edema in patients with osteoporosis with low vitamin D levels warrants evaluation for this coincidental condition in patients where etiology otherwise may be unclear (15). Predictable patterns of bone marrow edema are possible in the ankle following injury as has been noted in the knee typically resolving uneventfully or potentially persisting as a source of chronic pain (14,16).

Bone marrow edema may be considered to represent a part of a larger time-line of a pathological process exemplified by the early stages of AVN rather than a response to some form of bone stress. The pathological process of AVN can occur for a number of reasons not only secondary to the effects of an injury, but as a result of metabolic bone conditions such as neuroarthropathy, circulatory issues, blood dyscrasias, neoplasms, and infection. The time-line begins not with pathological stress with bone damage, but an interruption in bone blood supply that results in necrosis from avascularity. One of the initial bone tissue responses to this avascular event is with the production of edema within the bone even before any subsequent bone injury occurs. This bone marrow edema will typically be evident on MRI and not radiographs. As the AVN event progresses, regardless of etiology, stress on the surrounding bone may exaggerate the edema response. Eventually, structural bone compromise and fracture can occur as the dead avascular bone collapses unable to maintain integrity and strength against normal bone stress forces, not pathological trauma levels of force. The early MRI findings of bone marrow edema associated with AVN are similar to a bone bruise, but may also include evidence of necrosis. The MRI picture alone is typically too generic and nonspecific to aid a specific etiological diagnosis of bone marrow edema as a sign predicting impending AVN as opposed to the presence of a bone bruise alone.

The MRI identifies that bone marrow edema, regardless of etiology, is present. This prognostic sign of bone marrow edema, however, would be helpful in a clinical scenario where AVN may be possible or likely aiding early initiation of treatment preventing potentially harmful sequellae. Interpretation by the clinician of the relevance of the MRI finding of bone marrow edema is based on careful correlation of the presence and location of the bone marrow edema with the particular clinical situation. In the absence of specific etiological factors and demarcated areas of avascular bone, isolated bone marrow edema represents a self-limiting condition as opposed to avascular necrosis where bone marrow edema represents an early phase of a potentially destructive condition (15). The use of contrast when performing the MRI has been reported to aid and enhance this important differential diagnosis with vital clinical implications both in treatment and prognosis (18).

**CONCLUSION**

Bone marrow abnormalities are an intriguing clue to help explain persistent foot and ankle pain scenarios. They can be considered part of one of two bone response time-line possibilities, namely: a bone fracture injury type time-line or an AVN type time-line. Bone marrow abnormalities are only evidenced in the foot and ankle on MRI studies, not radiographs, bone scans, or CT scans. They represent a bone response process that is typically evidenced earlier in the pathological time-line on the MRI than would be seen on radiographs. They are then potentially early clues of impending bone pathology or stress responses. They may be asymptomatic and coincidental or a source of chronic foot and ankle pain. Their presence on MRI evaluation should not be ignored, but considered as a possible etiology for clinical pain symptoms or structural foot problems. Particularly in the foot and ankle for example, their presence may represent a secondary finding to post-traumatic joint instability or bone stress from a yet unappreciated foot condition such as a tarsal coalition, greatly aiding diagnosis.

Prolonged pain may be a result of lack of progression of healing with failure to resolve even after the actual etiology is successfully treated. Bone marrow abnormalities may be idiopathic as in the transient bone marrow edema condition, traumatic in origin as in a bone bruise, or pathological as in the first stages of an AVN event. Once identified, specific etiological diagnosis aids the direction of treatment. Treatment of the idiopathic or traumatic type...
bone marrow edema conditions such as bone bruise typically involves a fracture management approach of rest and immobilization with improvement in clinical symptoms by 3-4 months. Failure to respond may require treatment options typically considered for delayed or nonunion of bone healing including bone stimulation. Although no specific data is available, the logic of such treatment makes sense in bone healing terms especially in an attempt to avoid surgery as an option. Surgery, including fracture stabilization techniques, drilling and decompression, or resection with bone grafting, is rarely indicated for bone marrow edema management except in those situations where a pathological etiology may dictate a need such as seen in AVN.

Bone marrow edema conditions have been reviewed and a clinical case presented to highlight the need for a better understanding and appreciation of bone marrow edema and its useful role in clinical foot and ankle practice as well as a subtle etiology for chronic foot and ankle pain.

REFERENCES