CLINICAL VIGNETTE

Lateral Femoral Condyle Osteonecrosis and Subsequent Management with Prolotherapy Trial

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Case Presentation

A 75-year-old male with past medical history of hypertension, obstructive sleep apnea, and osteoporosis on alendronate 70 milligrams weekly for the past eleven months presented to pain clinic for new-onset left knee pain. The patient first noted left lateral knee pain while kneeling during a yoga class two months prior. The pain was severe, sharp, non-radiating, and only occurred when kneeling on any surface. The patient had no prior knee pain despite many years working as a mechanic and as a recreational gardener for several hours per day. Prior to this visit, left knee sleeve and capsaicin provided no pain relief during kneeling. On exam there was tenderness to palpation over the left lateral femoral condyle. All other knee exam findings were negative including: valgus and varus laxity/pain, anterior and posterior drawer, Thessaly test, McMurray's test, and Clarke's test. Ober's test was also negative. He was neurologically intact and had a left knee radiograph which showed sclerosis in the lateral femoral condyle possibly representing osteonecrosis. The patient was prescribed topical diclofenac and lidocaine patch as well as a prosthetic padded knee brace and was scheduled for left knee MR. The patient's primary provider was alerted for consideration of alendronate cessation given possible osteonecrosis and the patient was referred to Orthopedics. Two weeks later, left knee MRI showed a horizontal oblique tear of the posterior horn of the medial meniscus, osteonecrosis of the lateral femoral condyle, and chondrocalcinosis of the medial and lateral compartments. Orthopedics evaluated the patient and agreed that the pain was likely due to osteonecrosis as he had no medial knee pain that would correlate with medial meniscus pathology. The patient was recommended to continue conservative management given the osteonecrosis was well-contained and the joint spaces were well-maintained and was discharged from their clinic.

The patient was seen in follow-up five weeks later and reported continued focal left knee pain over the lateral femoral condyle with no change in physical exam. The patient was provided treatment options including physical therapy and further conservative management of osteonecrosis and was also offered a trial of prolotherapy to the region. After consent was obtained, prolotherapy was performed with a solution containing one mL of 1% lidocaine and one mL of 50% dextrose. The skin was prepped in standard semi-sterile fashion with Chloraprep and entered laterally with a 25-gauge 1.5-inch needle. The region adjacent to the left lateral condyle was peppered with this 2 mL injectate as well as a portion of the superior lateral collateral ligament. The patient tolerated the procedure well. On one-month follow-up, the patient reported improvement in left lateral knee pain with kneeling and direct weight bearing with a numeric pain rating of zero. He remained without left knee pain at follow up eight months later.

Discussion

Osteonecrosis, also referred to as avascular necrosis (AVN), is a known cause of pain and debility depending on the affected anatomical location. The commonly accepted pathogenesis of osteonecrosis involves interruption of bony vasculature with limited collateral blood supply resulting in bone necrosis.[1] Etiologies of osteonecrosis can be separated into atraumatic and traumatic categories. Atraumatic causes include dysbaric osteonecrosis, radiation injury, glucocorticoid use, alcoholism, systemic lupus erythematosus, hemoglobinopathies, and various others. Traumatic etiologies include fracture which directly disrupts bony vasculature, such as femoral neck fracture leading to femoral head AVN. Additional traumatic examples include tooth extraction causing AVN of the maxilla or mandible with concomitant bisphosphonate use which has been frequently reported.

Osteonecrosis associated with long-term bisphosphonate use was first described in 2003 in relation to the jaw.[2] The true incidence of disease is difficult to estimate due to measurement bias and possible under-reporting. It is widely agreed to be a rare complication, often associated with long-term bisphosphonate use following dental procedures. Incidence of medication-related osteonecrosis of the jaw is much lower in osteoporotic patients (0.004% – 0.2%) compared to cancer patients (0% – 6.7%) being treated with antiresorptive medications.[3] Osteoporosis patients on oral bisphosphonates complicated by osteonecrosis of the jaw had median bisphosphonate exposure of 4.4 years. AVN was almost never found in patients with less than one year of bisphosphonate use.

Lateral femoral condyle osteonecrosis is rarely reported and no reports of bisphosphonate-associated knee osteonecrosis could be found. Reports of bisphosphonate-related osteonecrosis generally involved the jaw (ONJ). The etiology is not well-understood and may be related to alteration of vascular endothelial growth factor versus early-onset osteomyelitic processes with inhibition of bone turnover.[4,5] Trauma is a

recognized risk factor for vascular disruption to areas of bone, however, repetitive microtrauma as as etiology is not well-established. We hypothesize that this patient, through his repetitive kneeling working as a mechanic and gardening/yoga hobbies, may have caused bony vasculature disruption via repetitive microtrauma with concomitant blockade of bone turnover for eleven months while taking alendronate that ultimately led to osteonecrosis.

The patient failed conservative management included bracing, home exercise/stretching, and oral and topical analgesics. He accepted a trial of prolotherapy. Prolotherapy is injection-based complementary and alternative therapy for chronic musculoskeletal pain. The National Institute of Health has funded two prolotherapy trials. The Centers for Medicare and Medicaid Services as well as the Veteran's Administration have determined existing prolotherapy literature to be inconclusive, yet list this as a treatment option.[6] The lack of evidence is due to the absence of formal practice guidelines with no standard treatment approach used in published studies.

More recently there is growing evidence showing possible efficacy in treating knee osteoarthritis in a single-arm uncontrolled study, a randomized controlled trial and a meta-analysis. All three studies showed significant improvement in pain and WOMAC scores compared to more conservative measures.[7-9] The efficacy of prolotherapy for knee osteoarthritis is largely attributed to cartilage regeneration. We found no studies on prolotherapy targeted at osteonecrosis.

Our patient experienced near-complete pain relief following one session of prolotherapy targeted to the structures surrounding the area of focal lateral femoral condyle osteonecrosis, including the more proximal insertion of the lateral collateral ligament (LCL). Our patient did not have any clinical or radiological evidence of soft tissue abnormality, involving the LCL, contributing to his pain. The LCL region was included during peppering of the area due to its proximity. Analgesia following prolotherapy injection to soft tissue overlying necrotic bone requires further review of possible mechanisms of prolotherapy. Prolotherapy is thought to cause cell death leading to a release of multiple factors including platelet derived growth factors, tissue growth factor-beta, epidermal growth factor, fibroblast growth factor, connective tissue growth factor, and insulin-like growth factor causing an overarching local inflammatory response leading to production of type one and three collagen.[10] It has been hypothesized that analgesic benefit of prolotherapy may be related to a direct effect on nerves. Prolotherapy may have a sclerosing effect on vessels feeding sensory nerves (vasa nervorum) as hypertonic dextrose can affect myelin lamellae as well as destroy unmyelinated nerve fibers.[11-12] This suggests a possible short- and long-term benefit of prolotherapy via effects on sensory nerve fibers.

It our patient, the mechanisms of analgesic benefit are inconclusive. Type one collagen is involved in bone health however, are unable to directly place prolotherapy injectate into necrotic bone. When considering the impact of prolotherapy on peripheral nerves, it is unlikely a one-time injection would lead to the long-lasting impact on nearby sensory nerves. Although the nearest sensory nerve, the superior lateral genicular nerve, may have been bathed by the prolotherapy injectate and this is one of three targeted nerves in interventional pain procedures such as radiofrequency ablation for chronic knee pain.

Though bisphosphonate-associated osteonecrosis is typically related to the jaw, this patient had no other risk factors for focal osteonecrosis aside from repetitive microtrauma which has not been clearly linked to AVN. His work as a mechanic, gardening several-hour per day and yoga may contributed to osteonecrosis based on repetitive kneeling. Regardless of the cause of his osteonecrosis, the patient clearly improved following targeted prolotherapy to his lateral knee. Prolotherapy has not been studied in bisphosphonate associated knee osteonecrosis study. We hypothesize analgesia was likely achieved via a neurolytic process rather than a regenerative process, but we cannot conclusively correlate this mechanism. This hypothesis needs further validation.

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