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Case Report

Extensive Osteonecrosis After Glucocorticoids: Clinical Response to Bisphosphonate

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Abstract

Osteonecrosis is a devastating complication of long-term glucocorticoid therapy that has been described in both malignant and nonmalignant diseases. Its incidence has been found to greater than 50% using magnetic resonance imaging in asymptomatic patients, thus osteonecrosis is likely underdiagnosed. Recent studies have suggested that treatment with bisphosphonates can improve pain and mobility and decrease bone marrow edema. We describe a patient with acute lymphoblastic leukemia who presented with debilitating osteonecrosis after treatment with prednisone for a total cumulative dose of 5100 mg. Magnetic resonance imaging revealed extensive infarcts of her bilateral tibiae and femora and left humerus, talus, and calcaneus consistent with osteonecrosis that had persisted for more than 2 years. Her severe knee, shoulder, and ankle pain was treated with 1 dose zolendronic acid. Despite a prolonged acute phase reaction, the patient's symptoms improved with near total resolution of pain.

Key Words: osteonecrosis, avascular necrosis, glucocorticoid, bisphosphonate, acute lymphoblastic leukemia

Endocrinologists are consulted for potential treatment of osteonecrosis arising from compromised blood supply resulting from bone or joint injury or sickle cell anemia or in patients requiring high-dose glucocorticosteroids. Now, as pediatric cancer patients live into adulthood, adult endocrinology practices will see more patients with osteonecrosis associated with glucocorticoid therapy of childhood cancer. We recently saw such a patient with extensive osteonecrosis and functional immobility due to pain.

Osteonecrosis can be a devastating complication of long-term glucocorticoid therapy in children but can be overlooked with standard X-ray imaging. It has been described in the setting of childhood malignant diseases including acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma as well as nonmalignant diseases such as systemic lupus erythematosus and in patients receiving bone marrow or renal transplants (1, 2). The incidence of osteonecrosis in children receiving glucocorticoids in the treatment of malignancy is substantial, reported in 22% in patients with non-Hodgkin lymphoma (3), 42% in those with Hodgkin lymphoma (1), and 59% in those receiving allogeneic hematopoietic stem cell transplants for ALL or acute myeloid leukemia. With ALL, depending on diagnostic imaging, incidence has been reported from 9% to as high as 72% (3, 4). This wide variation suggests osteonecrosis is likely underdiagnosed as it has been found on imaging in even asymptomatic patients (3, 5, 6). Symptomatic patients present with joint pain that can occur even at rest. After withdrawal of steroids, continued pain may herald articular surface collapse requiring joint replacement (6).

First-line treatment for osteonecrosis consists of conservative management with physical therapy, analgesics, and calcium and vitamin D supplements, and osteonecrosis may resolve spontaneously. Recent studies have suggested that treatment with bisphosphonates can improve pain and mobility and reduce bone marrow edema (6, 7). We describe a patient 2 years into remission after treatment for ALL who presented to us with debilitating osteonecrosis in multiple joints and who received symptomatic relief from bisphosphonate therapy.

Case Presentation

In June 2021, a 20-year-old woman was referred to us for management of osteonecrosis; after menarche age 12, she was started on oral contraceptives at 15 due to menorrhagia. Her family history included spina bifida and ankle deformity in her mother and osteoporosis in her great-grandmother. Her personal medical history included high-risk B-cell ALL with central nervous system involvement diagnosed in December 2017. She was treated with chemotherapy (combination of vincristine, cytarabine, methotrexate, daunorubicin, pegaspargase, cyclophosphamide, and mercaptopurine) and high-dose prednisone [50 mg twice daily for a month at initial diagnosis, followed by prednisone, about 35 mg (20 mg/m^2 estimated body surface area) twice daily 5 days every month between September 2018 and March 2019, for a total cumulative dose of 5100 mg]. In February 2019 she complained of right knee pain and swelling. Radiography revealed an ill-defined heterogeneity of the right proximal tibia and fibula concerning for bone marrow infarcts. Follow-up magnetic

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resonance imaging (MRI) revealed an extensive serpentine rim of peripheral T1 hypointensity and T2/short tau inversion recovery hyperintensity encompassing the same area, which confirmed intramedullary bone infarcts consistent with osteonecrosis (Fig. 1, with normal comparison). Gadolinium contrast images showed areas of increased T2 which reflect the presence of water in tissue (Fig. 2), also referred to as short tau inversion recovery or STIR. Increased gadolinium contrast in the same distribution of T1 signal intensity suggests the area is perfused and likely viable. After the diagnosis of tibial and femoral osteonecrosis, glucocorticoid therapy was discontinued in March 2019.

By March 2020 the patient was considered to have entered oncologic remission. However, her right knee pain persisted, and in November 2020 she complained of new pain involving her left knee and ankle. MRI findings of the left lower limb showed osteonecrosis of the proximal tibia and distal femur, distal tibia, anterior and central talus, and posterior calcaneus. She was treated supportively with acetaminophen, oxycodone, and physical therapy. Continued pain, now in the left shoulder, led to referral to our clinic for an approach to persistent multijoint involvement that greatly limited her mobility.

To assess the burden of disease, we obtained a technetium (Tc-99 m methylene diphosphonate) whole-body scan. This revealed radiotracer uptake within the left humeral head, distal femora, right greater than left proximal tibia, and right greater than left ankle and hindfoot (Fig. 3). There were also subtle foci of uptake in the distal femora and proximal tibiae.

Treatment, Outcome, and Follow-Up

Given our patient's extensive disease and persistent pain, we elected to treat her with a 1-time infusion of zolendronic acid (5 mg). She developed low-grade fevers and flu-like symptoms for 3 to 4 days and noted worsening of pain in multiple

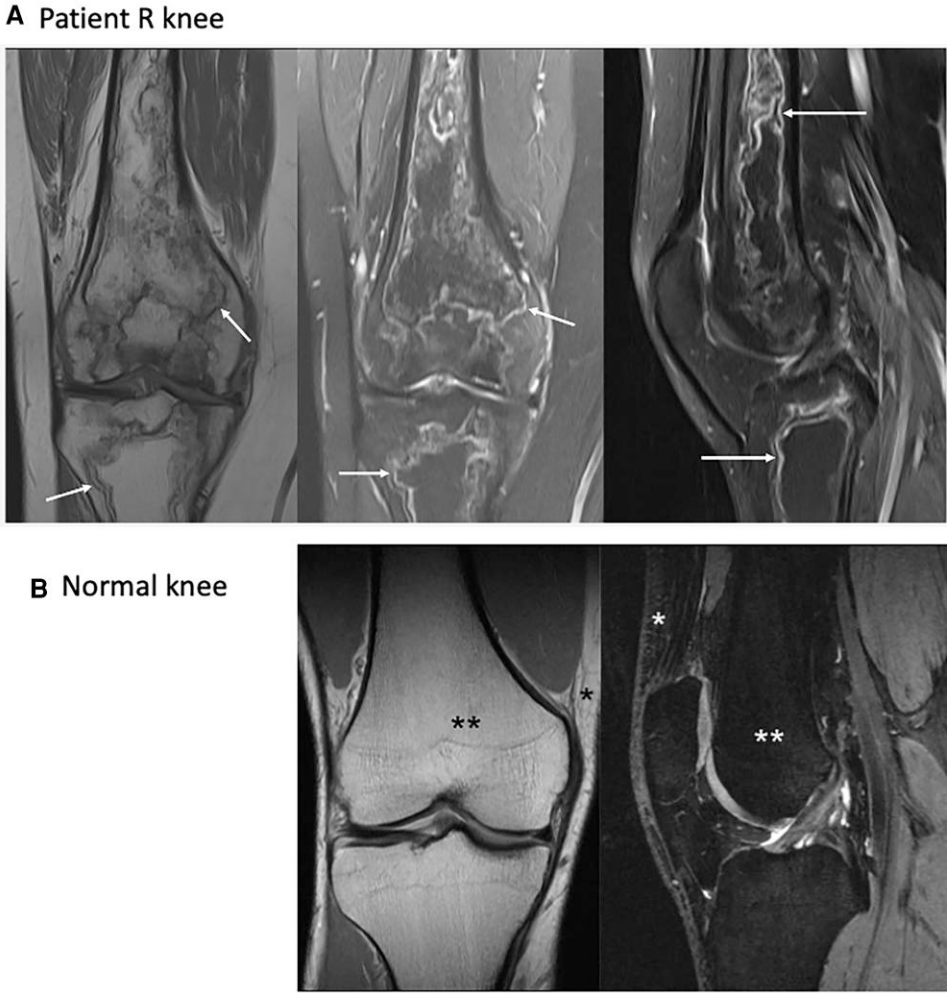

Figure 1. Patient and comparison normal knee images. (A) Coronal T1-weighted (left) and fat-suppressed T2-weighted coronal (center) and sagittal (right) magnetic resonance images of the right knee. The T1-weighted coronal image shows abnormal, decreased signal intensity in the distal femur and proximal tibia representing osteonecrosis, extending down to the subchondral bone of the femoral condyles at the knee. The dark, serpentine margins on the T-1-weighted image (arrows) represent the edges of the infarcts. The coronal and sagittal T2-weight images show white bands of increased T2 signal intensity (arrows) paralleling the margins of the infarcts demonstrated on the T1-weighted images, the "double line sign." The bands of increased T2-weighted signal intensity represent granulation tissue and viable bone. (B) Coronal T1-weighted (left) and sagittal STIR (right) magnetic resonance images of a normal knee show homogenous marrow signal intensity. On the T1-weighted image, the marrow signal intensity is bright (black **) and comparable to that of subcutaneous fat (black *). On the STIR image, the signal intensity from the bone marrow is depressed (white **), again comparable to subcutaneous fat (white *).

Abbreviations: STIR, short tau inversion recovery.

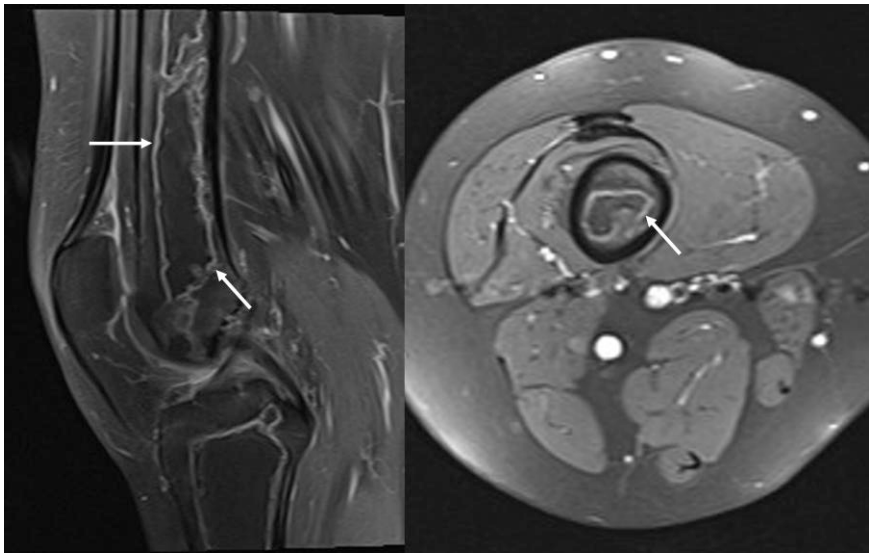

Figure 2. Gadolinium contrast images. Fat-suppressed T1-weighted sagittal (left) and transverse (right) images obtained after the administration of intravenous gadolinium contrast. White, serpentine bands of increased signal intensity (arrows) represent hyperemic and viable bands of granulation tissue and correspond to similar bands of increased signal intensity on the fat-suppressed T2-weighted images.

joints lasting 2 weeks. Within several months her symptoms improved significantly, and she reported that her pain had nearly resolved. Along with this she became much more functional and started exercising with a trainer 5 days each week.

A repeat MRI of the right knee obtained 6 months after the bisphosphonate treatment suggested unchanged radiological disease. A repeat total-body bone scan was also unchanged except for possible decreased uptake at the ankles.

Discussion

Osteonecrosis is a destructive complication of long-term glucocorticoid therapy used in the setting of both malignant and nonmalignant diseases as well as transplantation (2). Its incidence is thought to be as high as 72% in the pediatric ALL population, but it is likely underdiagnosed (3–6). Risk factors for osteonecrosis during ALL treatment include older age, female sex, obesity, and greater cumulative doses of corticosteroids (3, 5, 8, 9). A meta-analysis suggested that treatment with a cumulative dose of corticosteroid equivalents >10 g was more than 2 times as likely to be associated with osteonecrosis (odds ratio 2.4, 95% CI 0.8-6.4) (2). Our female patient, diagnosed with ALL when she was 18 years old, had a cumulative dose of slightly over 5 g but daily doses were in excess of 70 mg, all which put her in a higher risk category for developing osteonecrosis. It is thus important to highlight that osteonecrosis, while rare, should be considered in the differential diagnosis of patients who have received high-dose glucocorticoids and present with nonspecific musculoskeletal concerns; often such concerns might be attributed to secondary adrenal insufficiency or other conditions.

Maturing bone, as compared to prepubertal or adult bone, is thought to be more susceptible to osteonecrosis (9). The local pathogenesis is thought to be multifactorial, incorporating vascular impairment and abnormal osteocyte and intramedullary adipocyte activity (2, 9). Increased estrogen concentrations increase the risk of thromboembolism via procoagulatory effects and increase bone remodeling with consequent demand for increased blood supply. Further, increased growth hormone and insulin-like growth factor 1 activity during puberty leads to increased metabolic activity and oxygen consumption, putting tissue at increased risk in the setting of hypoxia. Insufficiency of vascular supply at distal bones contributes to osteonecrosis, and this can be further impaired by intraosseous pressure (8). The open physes of prepubertal children are putatively able to release pressure, while the older adolescent with fused epiphyses may have a more compromised local vascular system. Osteonecrosis has a predilection to involve of joints of the lower extremity, with the most commonly affected sites being the knees (distal femur and proximal tibia), hips (proximal femur), and ankles (distal tibia) (1, 6). Interestingly, convex articular surfaces—being subject to convergent forces—have also been shown to be at higher risk compared to concave surfaces that are subject to divergent forces; divergent forces are thought to be less likely to cause vasoocclusion.

Radiographs obtained to evaluate joint pain are insufficient to rule out osteonecrosis prior to joint failure, and MRI is the gold standard for diagnosing osteonecrosis (9). MRI demonstrates the early focal serpentine signal abnormalities, which may be accompanied by diffuse edema (see Fig. 1). Nevertheless, the significance of MRI findings in asymptomatic individuals remains unclear, and currently there are no recommendations to perform MRI on multiple joints in these patients. Further, the precise role of MRI in evaluating progression of disease and in correlating with pain remains imprecise.

Several approaches have been used in the treatment of osteonecrosis, including a conservative approach with physical therapy and analgesics, a pharmacologic approach with antiresorptive agents (specifically bisphosphonates), and a mechanical approach with shock wave therapy (6, 7, 10). A meta-analysis of the effect of shock wave therapy by Al-Abbad et al found a possible modest reduction in osteonecrosis lesion size on MRI, but the studies only considered osteonecrosis of the femoral head and excluded patients with malignancy or late Association Research Circulation Osseous stages of disease (10). They speculated that shock

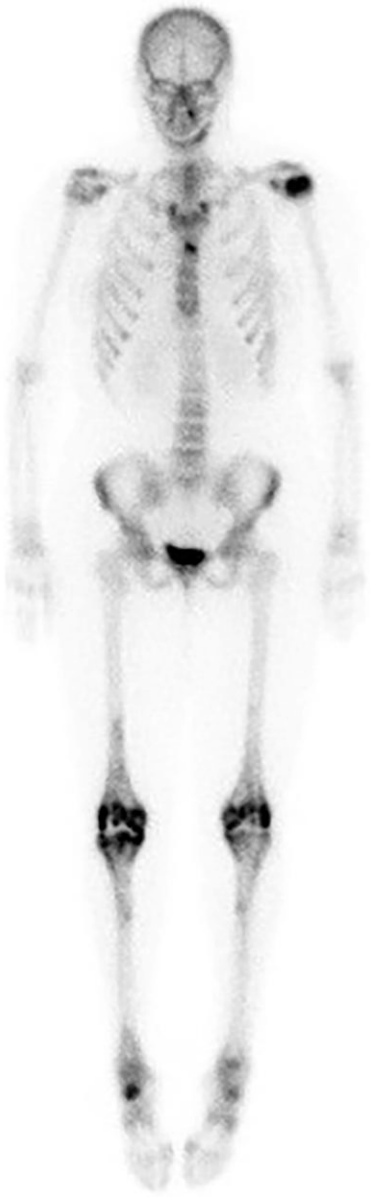

Figure 3. Bone scan total body assessment. A radionuclide Tc-99 m methylene diphosphonate bone scan shows prominent increased osseous remodeling in the distal femora, proximal tibiae, left proximal humerus, distal tibiae, and right talus representing foci of osteonecrosis.

wave therapy might offer a better alternative than surgery, at least in early Association Research Circulation Osseous stages, given the high cost and risk of complications associated with surgery. Finally, to treat pain, patients may progress to joint replacement.

Our patient responded favorably to treatment with zolendronic acid. After an intense and lengthy acute phase reaction greater than expected in osteoporosis patients, her symptoms subsided. Her pain and mobility improved greatly over the next few months, and, despite the continued presence of osteonecrosis on MRI and nuclear images, she is now able to be physically active. A meta-analysis found that bisphosphonates, when compared to calcium, vitamin D supplements, and physical therapy, led to improved mobility (66% vs 27%, $P = 0.02$) and no or only mild to moderate pain (83% vs 36%, $P < 0.001$) (6). Follow-up MRI showed resolution in only 28% of cases. In contrast, a recent trial assessing the efficacy of zolendronate vs placebo in the treatment of nonmalignant bone marrow lesions in adults found a 65% reduction in the lesion volume in patients receiving zolendronic acid compared to a 14% increase in the placebo group ($P = 0.007$), which was associated with decreased pain (7). Our patient had a significant clinical response with bisphosphonate therapy but no apparent response on MRI, although it is possible that we were not able to adequately quantify changes to bone marrow edema. As such, while it is known that bisphosphonates may help with pain and mobility in osteonecrosis (6), our case suggests that MRI imaging should not be used to judge response to treatment. It is known that MRI findings in other settings, such as healing fractures, may persist well after a patient experiences clinical improvement.

Our patient's response raises the question as to whether bisphosphonate therapy may help in the treatment of bone pain experienced by patients with other conditions such as sickle cell disease. It should be noted that MRI findings in osteonecrosis in patients with sickle cell disease are different from those in patients with glucocorticoid-associated osteonecrosis. Osteonecrosis in patients with sickle cell disease is often noted on MRI to be more diffuse with larger lesions. Regardless, the significance of MRI findings in asymptomatic individuals remains to be determined.

Ultimately our patient demonstrated significant clinical improvement in her osteonecrosis-related pain with bisphosphonate therapy. While it remains to be seen how our patient's clinical course progresses, including whether she will need joint replacement, the improvement in her symptoms thus far with medical therapy alone is encouraging. Bisphosphonates should be considered in the treatment of bone pain in other conditions; further investigation is needed.

Learning Points

- Osteonecrosis is a devastating complication of long-term glucocorticoid therapy.
- Osteonecrosis is likely underdiagnosed given it has been found on imaging in asymptomatic patients. Consultation with radiology can be critical.
- Bisphosphonates can significantly improve pain and mobility in osteonecrosis.

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Author Contributions

All authors made individual contributions to authorship. K.S. and J.E.R. were involved in the diagnosis and management of this patient and manuscript submission. J.B.R. was involved in radiographic analysis and manuscript submission. All authors reviewed and approved the final draft.

Disclosures

The authors have no conflicts of interest to disclose.

Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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