Bilateral extensive steroid-associated osteonecrosis (SAON) of femur, tibia and patella: Successful early management with combined antiresorptive and anabolic bone agents

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\textbf{ABSTRACT}

\textbf{Aim of the work:} To present a case of bilateral extensive steroid-associated osteonecrosis (SAON) of femur, tibia and patella that was successfully managed with combined antiresorptive and anabolic bone agents.

\textbf{Case presentation:} A 38-year-old female patient encountered an aggressive coronavirus disease 2019 (COVID-19) infection and was given systemic steroids for six months. The patient then began to experience bilateral lower limb pain. Tenderness over the knee joint margins was found, as well as tenderness of the lower end of the femur, upper tibia, and patella on both sides. The initial plain x-ray of the lower limb bones revealed subtle areas of sclerosis at the proximal metaphysis of tibial bones. The patient did not improve despite stopping steroids and repeated courses of simple analgesics, and the pain became progressive and more intense, to the point where the patient was unable to bear any weight and became wheelchair bound. Magnetic resonance imaging (MRI) was done revealing extensive osteonecrotic lesions involving the distal metaphysis of the femur with posterior extension into the medial and lateral condyles abutting the articular surfaces. Two anti-osteoporotic drugs were used; alendronate, used weekly to inhibit osteoclastic activity and limit the progression of the osteonecrotic lesions and teriparatide, an anabolic agent that increases osteoblasts, resulting in new trabecular and cortical bone growth. Clinical improvement, pain and ambulation, occurred after one month of initiation of treatment and follow up MRI study after 10 months showed marked radiological improvement.

\textbf{Conclusion:} Combined antiresorptive and anabolic bone agents remarkably reversed SAON.

1. Introduction

Osteonecrosis (ON), similar ischemia/necrosis in other organs, is caused by a disruption in bone blood supply. It can happen in either the medullary cavity or the cortex. The femoral head, femoral and tibial metaphysis, proximal tibia, talus, and scaphoid are common sites for ON.\textsuperscript{[1]} Magnetic resonance imaging (MRI) is widely regarded as the most specific and sensitive imaging modality for detecting and tracking the progression of ON. In addition, the degree of surrounding bone marrow edema (BME) correlates well with the patient’s symptoms.\textsuperscript{[2]} A recent study used color Doppler ultrasound to assess and monitor hip vascularity deterioration in systemic lupus erythematosus (SLE) patients, particularly those on steroids and at risk of developing ON.\textsuperscript{[3]} Another study concluded that nephritis; serositis, GI involvement, arthritis, and steroid use are important predictors of advanced ON of the femoral heads in SLE patients.\textsuperscript{[4]} Nonetheless, in patients with primary antiphospholipid syndrome (APS), transient BME of the hip may complicate the disease course; the latter is currently considered a
prodrome for ON [5].

There are numerous causes of ON most commonly related to trauma, corticosteroids, and idiopathic. Imaging of osteonecrosis is frequently diagnostic with a serpentine rim of sclerosis on radiographs, and maintained yellow marrow at MR imaging with a serpentine rim of high signal intensity (double-line sign) on images obtained with long repetition time sequences. On the other hand, Transient Regional Osteoporosis (TOH) of the hip is a serious hip that has the potential to progress to ON and femoral head collapse in case of missed or delayed diagnosis [6]. On MRI, it is distinguished by the absence of a double-line sign. Recently, once-weekly oral Alendronate has been shown to be an extremely effective treatment option for TOH with extensive bone marrow edema (BME) pattern. [7].

Steroid-associated osteonecrosis (SAON) is a common side effect of long-term corticosteroid use for a variety of medical conditions, most notably autoimmune disorders. There are several proposed pathophysiologies for SAON, all of which have negative effects on various bone elements such as the bone marrow stem cell (BMSC) pool, bone matrix, cell apoptosis, lipid metabolism, and angiogenesis [8]. It was recommended early that osteoblast activity should be stimulated and osteoclast activity be inhibited as soon as possible to prevent the collapse of an osteonecrotic femoral head. [9].

In this report, we present the successful treatment of extensive SAON involving the lower femur, upper tibia, and patellar bones bilaterally. Two anti-osteoporotic drugs were used; alendronate used weekly to inhibit osteoclastic activity and thus limit the extension and progression of the osteonecrotic lesions as well as teriparatide, an anabolic agent that increases osteoblast survival and number, resulting in new trabecular and cortical bone growth. The case is detailed, and the radiological improvement documented by MRI is presented.

2. Case presentation

A 38-year-old female patient developed an aggressive coronavirus disease 2019 (COVID-19) infection and was treated with systemic steroids for six months based on recommendations that systemic corticosteroid therapy improves clinical outcomes and lowers mortality in hospitalized COVID-19 patients who require supplemental oxygen. Six months after starting steroids, the patient began to experience bilateral knee, leg, and lower thigh pain, with the latter being more severe on the left side. Tenderness over the knee joint margins, as well as tenderness over the lower end of the femur, upper tibia, and patella bones, was found on both sides, with the left side being more intense. The initial plain x-ray of the lower limb bones revealed subtle areas of sclerosis at the proximal metaphysis of tibial bones. Despite discontinuing steroids and repeated courses of simple analgesics, the patient’s pain worsened and became more intense, to the point where the patient was unable to bear any weight and was wheelchair bound.

An MRI was initially performed; full study on the left side and a limited on the right. MRI of both knees revealed bilateral multiple areas of bone infarction involving the distal metaphysis of the femur with posterior extension into the medial and lateral condyles abutting the articular surfaces, with more anterior extension at the weight-bearing regions of the medial femoral condyles (Figs. 1-3). The lesions also had partially ill-defined serpentine outlines and were situated at the proximal metaphysis of the tibia, the patella, and the distal metaphysis of the femur (Fig. 1a and b, and Fig. 2a – c, respectively), the latter lesions were encircled by BME. Identical MRI distributions and findings

![Fig. 1. MRI of the left knee.](image)
were also seen on the right side (Fig. 3a). Furthermore, femoral involvement was also noted anteriorly at the patello-femoral articulations. Similar lesions were seen at the proximal tibial metaphyses with relative sparing of the subarticular surfaces. Bone infarcts were also seen at both patellae, on both sides being more aggressive on the left side.

After establishing the diagnosis of extensive SAON of both lower
limb bones, the patients was treated with two anti-osteoporotic drugs. The first “Alendronate” on a weekly basis (70 mg/week/PO) to inhibit osteoclastic activity and thus limit the extension and progression of the osteonecrotic lesions and the second teriparadate, (20 mcg SC daily) an anabolic osteoporosis medication that increases osteoblast survival and number, resulting in new trabecular and cortical bone growth. In addition to daily calcium and active Vitamin-D supplements, protective weight-bearing was recommended for the first month.

Our rationale was to use alendronate to inhibit osteoclastic activity and obtain defined margins of active osteonecrotic lesions and avoid their expansion, and teriparadate to induce reparative osteogenesis within the active osteonecrotic lesion. Based on the clinical improvement in pain and ambulation that was seen after one month of starting the aforementioned lines of treatment, an ongoing success in achieving the goals was emerging. Most importantly, a follow-up MRI after 10 months of treatment showed a respectable radiological improvement, with axial T1 images demonstrating that the lesions became well-defined with no extensions and the size has shrunk. (Fig. 1d – f and Fig. 2e – h). Similar improvement was also observed in the right lower limb before and after treatment (Fig. 3).

An in-depth analysis of the MRI changes revealed initial bilateral osteonecrotic lesions with ill-defined margins especially at the interface of the surrounding bone marrow (intermediate signal intensity on T1 and T2 sequences) (Fig. 1a – c and Fig. 2a – d) indicative of non-sclerotic active margins. Following treatment; the lesions’ boundaries became well-defined (low signal intensity) (Fig. 1d – f and Fig. 2e – h) indicating new bone formation with sclerotic edges, and associated mild regression of the lesions’ sizes more evident at both patellae. Furthermore, the initial MRI images showed significant BME surrounding the infarcts (increased signal intensity) on fat saturation and short tau inversion recovery (STIR) images (Fig. 2e – h) more noticeable at the tibial bones and the complete resolution of BME on follow-up provides further evidence of radiological improvement. Nonetheless, the central portions of the bone infarcts displayed heterogeneous signal intensity on all pulse sequences which turned more homogenous following treatment due to decreased edema and increased fat signal on T1, T2 and fat saturated images.

3. Discussion

In this report, a successful treatment of bilateral extensive SAON involving the lower limb bones (lower end of femur, upper tibia and patellar bones) is described. The patient was treated with two anti-osteoporotic medications with different mechanisms of action, with a successful outcome in terms of pain control as well as radiological improvement by MRI.

After establishing the diagnosis of extensive SAON of both lower limb bones, two anti-osteoporotic drugs were used, alendronate to inhibit osteoclastic activity and thus limit the progression of the osteonecrosis and teriparadate, an anabolic osteoporosis medication. Based on the clinical improvement in pain and ambulation that started after one month encouraged to continue in order to successfully achieve the goal. The follow-up MRI confirmed the improvement after 10 months of combination therapy.

Osteonecrosis is a disabling clinical disease entity characterized by the death of osteocytes and bone marrow, followed by resorption of the necrotic tissues and the formation of new but weaker osteous tissue, resulting in a progressive destruction of bone architecture, subchondral fracture, and joint collapse, most commonly at the femoral head, and finally loss of joint function. [10]. Relative to SAON, there are various pathophysiologies that have adverse effects on various bone elements such as the bone marrow stem cell (BMSC) pool, bone matrix, cell apoptosis, lipid metabolism, and angiogenesis. Patients who received glucocorticoids had reduced trabecular width and an increased number of apoptotic osteoblasts and osteocytes. In SAON, there were two repair types for ON lesions. Reparative ON refers to the formation of appositional bone with osteoblast-like cells around a necrotic lesion, whereas destructive repair refers to granulation tissue creep associated with necrotic bone resorption [11].

Relative to the treatment strategy for the current case, combination therapy of two anti-osteoporotic agents with different mechanisms of actions was started. Alendronate is a bisphosphonate that prevent osteoclastic bone resorption and is effective in the treatment and prevention of postmenopausal and steroid-induced osteoporosis as well as Paget’s disease. The drug is uptaken into bone, where it exerts its pharmacological activity, with long residence in the skeleton. Thus, alendronate corrects the underlying imbalance in skeletal turnover present in several diseases [12]. Alendronate would slow down the progression of osteonecrotic lesions by directly inhibiting osteoclastic activity. Abnormal osteoclastic activity in SAON of the femoral head contributes to bone structural integrity loss and subchondral fracture [13]. The drug binds to hydroxypapitate crystals in bone, which inhibits osteoclast-mediated bone resorption and reduces bone matrix breakdown. Notably, [14]. Furthermore, in patients receiving long-term prednisone, denosumab and alendronate had similar beneficial effects on hip and femoral neck bone mineral density (BMD) [15]. Nonetheless, alendronate treatment causes an early, dose-dependent and reversible inhibition of skeletal resorption, which can be tracked clinically with biochemical markers and eventually reaches a plateau [12].

Teriparadate, an analog of parathormone (PTH), binds through the N-terminal moiety to PTH type 1 receptors (PTH-1R). PTH-1R is a G-protein coupled receptor expressed on the surface of various cells, most importantly are the osteostals, osteocytes and renal tubular cells. Following ligand binding to the receptor, both Gs-mediated activation of adenylate cyclase and Gq-mediated activation of protein kinase C (PKC) occur [16,17]. Adenylate cyclase catalyzes the generation of the secondary messenger CAMP, which ultimately activates protein kinase A (PKA). Although PTH activates both PKA- and PKC-dependent signaling pathways, the PKA-dependent pathway is the primarily used one for its anabolic and catabolic effects on bone [17].

Importantly, teriparadate was used to induce repair within the osteonecrotic bone lesions by increasing osteoblast survival and number, resulting in new trabecular and cortical bone growth. Thus concept was supported by the anabolic effects of intermittent PTH (teriparadate) mediated by the upregulated transcriptional expression of pro-osteoblastogenic growth factors such as insulin-like growth factor 1 (IGF1) and fibroblast growth factor 2 (FGF2); the modulation of the wnt/beta-catenin osteoanabolic signaling pathway by down-regulating the synthesis of the wnt-antagonist sclerostin and by the increased expression and activity of Runx2 – A transcription factor essential for differentiation of osteoblasts [16]. Accordingly, teriparadate significantly increased cancellous bone volume and connectivity, improved trabecular morphology with a shift toward a more plate-like structure, and increased cortical bone thickness in postmenopausal women with osteoporosis [18]. These pathways eventually hastened the reparative osteogenesis in aggressive osteonecrotic lesions [16] as seen in this patient. Furthermore, the analgesic effects of teriparadate on bone is an important management line [19]. Aside from these logical backgrounds, the most solid evidence was the radiological improvement seen in MRI before and after treatment.

Despite the fact that combining two antiresorptive medications is rarely justified, if ever, various anabolic and anti-resorptive therapies have been combined in an attempt to achieve superior bone mass and strength effects compared to monotherapy. However, it is postulated that “teriparadate” in combination with antiresorptive agents may have additive and synergistic effects in SAON. The latter rationale was remarkably effective in this patient, as evidenced by the clinical and, more importantly, radiological improvement of the MRI findings after treatment and the bottom line is that “the patient is our book”. A larger scale longitudinal study is warranted to confirm the reached results.

In conclusion, extensive SAON of the femur, tibia, and patella was...
successfully treated with antiresorptive (alendronate) and anabolic bone (teriparatide) agents achieving bone healing and radiological remission as documented by MRI 10 months after combination therapy. To the best of our knowledge, SAON has never been treated with such a combination of antiresorptive and anabolic bone agent. Such combination may be a top gun in treating such an aggressive disease process, particularly in those receiving maintenance steroids and developing extensive osteonecrotic lesions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References