REVIEW ARTICLE

BISPHOSPHONATE INDUCED ATYPICAL PROXIMAL FEMORAL FRACTURE: "DOUBLE EDGE DAGGER" RADIOLOGICAL AND SCINTIGRAPHY FINDINGS

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Bisphosphonates have been used for more than two decades for the treatment and prevention of osteoporosis. Bisphosphonates act by inhibiting osteoclasts to slow bone resorption through apoptosis.[1] Large body of data have shown that bisphosphonate can improve bone density and reduce the risk of fracture in patients with a reduced bone density like osteoporosis and metastatic bone disease. Most commonly used agents are alendronate, pamidronate, zolendronic acid, pamidronate, risedronate, ibandronate and etidronate. They are administered either orally or intravenously with variable frequency. Pamidronate was the first intravenous bisphosphonate and along with zolendronic acid have been approved by FDA also for treatment of cancer related hypercalcemia and Paget's disease.[2]

These drugs reduce the risk of osteoporosis-related fractures as quickly as six months after institution of the drug. Although there is a difference of efficacy between different types of bisphosphonate, the efficacy of bisphosphonate is predominantly dependent on the compliance to bisphosphonate.[3] A meta-analysis demonstrated that zoledronic acid was most effective for reducing vertebral fractures and improved compliance and poor gastrointestinal absorption of oral bisphosphonates were suggested as possible explanations.[4]

Oral bisphosphonates are known to induce serious esophagitis, gastritis and diarrhea.[5] Patients with known esophageal disease (e.g., achalasia, stricture, Barrett's esophagus, severe reflux and scleroderma) should avoid taking oral bisphosphonates. After intravenous administration, most common side effects areiritis, muscle aches and fever which is related to cytokine release and is reversible on discontinuation of drug. Cyclical etidronate (Didronel) may be considered in patients with poor tolerance to alendronate as it has fewer upper GI side effects but higher incidence of lower GI side effects than alendronate. Bisphosphonate-related osteonecrosis of jaw (BRONJ) is a condition found in patients who have received intravenous and oral forms of bisphosphonate therapy.[6] BRONJ is thought to be caused by trauma to dentoalveolar structures that have a limited capacity for bone healing due to the effects of bisphosphonate therapy.[6]

In spite of their clinical benefits, long-term use of bisphosphonate has been linked to occurrence of atypical femoral fractures (AFFs). Recent literature show lower absolute incidence (1 in 1000 treated Vs 0.02 per 1000 untreated women) but favors an association between long-term bisphosphonate use and incidence of AFFs.[7] Although the pathogenesis of AFFs has not been fully understood, long-term suppression of bone remodeling would cause a deterioration of the bone microarchitecture, reduce the bone repair process and lead to the accumulation of microdamage resulting in the progression of AFFs.[8]

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Most common clinical presentation of AFF is pain in the affected thigh or groin and ultimately complete and significantly displaced fracture of proximal femoral shaft. In the pre-complete fracture phase, radiographic findings are usually subtle which could be easily overlooked. Typically, insufficiency fracture lies within lateral cortex of proximal femur as transverse fracture line through a localized area of thickening at lateral aspect of cortex giving a beak appearance (Fig.1). This appearance mimics that of tibial striation or stress fracture seen in anterior cortex of the tibia. Underlying nature of insufficiency fracture is also evidence on radiographs of complete fracture of femur prior and after open reduction and internal fixation (Fig.2). Prior data suggest that a significant percentage of patients with evidence of cortical stress in this region or insufficiency fracture have similar findings in the contralateral femur as well (Fig.1 and 3). Involvement of the contralateral femur varies in literature, ranging from 20% to 64% and it is advisable to image contralateral femur as well.[9]

Radionuclide bone scan using Technetium-99m Methylene Diphosphonate (^{99m}Tc-MDP) has high sensitivity to detect AFF due to its characteristic appearance. Typical findings are focal areas of enhanced tracer uptake in blood pool and static images along the lateral cortex of proximal femur (Fig.3). This explains binding of radiotracer (MDP) to hydroxyapatite crystals in proportion to increased local blood flow and osteoblastic activity at site of incomplete insufficiency fracture (Fig.3). Bones scan can detect asymptomatic insufficiency lesion in contralateral femur which are not appreciable on plain

Figure 1: (A) Bone scanintigraphy showing focal osteolastic lesions involving lateral cortices of bilateral priximal femur in lady with history of 3 years bisphosphonate tremanet and recent bilateral groin pains. **(B & C)** Plain radiograph of both femur revealeding transverse fracture lines through a localized lateral cortical thickening giving a typical beak appearance

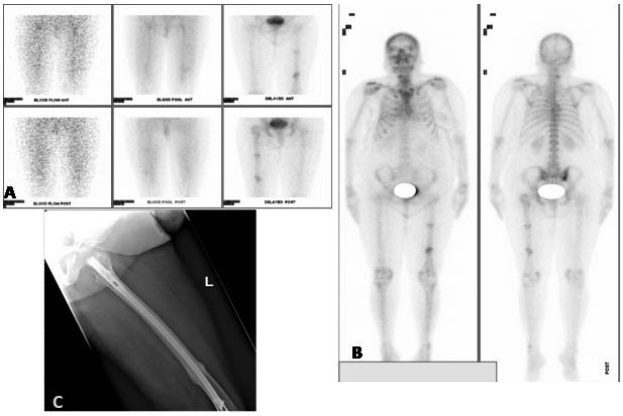

Figure 2A & B: Dynamic ^{99m}Tc MDP bone scintigraphy showing two active osteoblastic lesions at in left femur involving both cortices in a patient with complete internally fixed left femoral shaft fracture. **(C)** Internally fixed left distal femur fracture with persistent fracture line and cortical thickening (delayed union) and no morphological abnormality in proximal femur as noted on bone scintigraphy (likely new evolving insufficiency fracture).

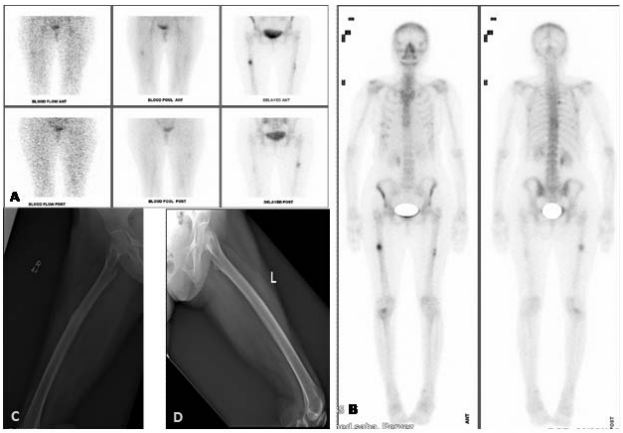

Figure 3A & B: Dynamic 99mTc MDP bone scintigraphy showing active osteoblastic lesions involving lateral cortices of both femur (advanced lesion on right and early evolving on left) in a patient has been on bisphosphonate treatment for 4 years presented with right thigh pain. **3(C):** Right femur plain X-ray in same patient showing incomplete atypical proximal fracture concomitant with osteoblastic lesion visible on bone scintigraphy. **3(D):** Left femur plain X-ray in same patient showing no concomitant radiological abnormality in middle 1/3rd of lateral cortex.

radiograph as well (Fig.3). A negative bone scan in patient with focal thickenings of femoral cortexon plain radiographs favors an inactive scar after a stress reaction.[10] However, bone scan with incomplete AFF has low positive predictive value for impending complete fracture.[11]

Differential diagnosis of AFF includes stress fractures (due to repetitive trauma of normal bone), pseudofractures of osteomalacia (Vitamin D deficiency) and pathological fracture. Stress fractures usually occur in athletes and military recruits typically involving medial cortex in the proximal femur as it has attachments of vastus medialis and adductor brevis.[12] Conversely, bisphosphonate insufficiency fractures occur in elderly involving lateral cortex. Stress fractures on radiograph show foci of periosteal reaction with an obliquely oriented linear lucency within the medial cortex (Fig.4).[13] While insufficiency fractures typically present as focal cortical thickening with a transverse lucency within the lateral cortex. *Pseudofractures or looser zones of osteomalacia* also show a transverse lucency through medial cortex of femur, often multiple

Figure 4: Focal periosteal thickening with minimal lucency along the medial cortex of right femur in an athlete representing stress fracture (white arrow).

but without significant associated cortical thickening (Fig.5).[14] *Pathologic fractures* of the proximal femoral diaphysis are nearly always transverse and typically are due to metastatic disease, Paget disease, or fractures through preexisting looser zones. When they are caused by metastatic disease, these fractures

Figure 5: Looser zone involving medial cortex of proximal femur characteristic for osteomalacia (arrow).

show poorly defined lucent margins, an aggressive bone marrow pattern of destruction, and endosteal scalloping.[14] *Fractures related to Paget disease* show one or more fracture lucencies projecting through the cortex along the convex margin of the femur; however, concomitant deformity of the femoral shaft is also present.

Bisphosphonate therapy has been an established and effective therapeutic option to prevent osteoporotic hip and other fractures but undeniable plethora of side effects ranging from esophagitis, iritis, jaw necrosis and atypical femoral fractures. AFFs are not very common but present pain, incomplete insufficiency fracture to complete fracture. These fractures have higher tendency of delayed union or non-union due to bisphosphonate induced reduced bone remodeling. So beyond any doubt benefits of bisphosphonate outweigh its risks but one should not forget it is a “Double Edge Dagger”.

Conflict of Interest: Authors declare none.

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