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Case Series

Zoledronic Acid-Induced Lesions Mimicking Metastasis in Patients with Bone Cancers

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Abstract

Zoledronic acid (ZA) is used to treat osteoporosis, hypercalcemia, metabolic bone disease, cancer induced bone disease, and Paget's disease of bone. In cancer patients with bone metastasis, it can decrease pain and occasionally induce shrinkage. For primary bone tumors, such as osteosarcoma and Ewing sarcoma, zoledronic acid has been trialed as part of combination chemotherapy strategy in high-risk patients. Osteonecrosis of the jaw is a well described side effect of ZA, but osteonecrosis of other bones is very rare. We describe three patients with relapsed primary bone tumors on zoledronic acid who had presumed relapse with new bony metastasis, that was subsequently contradicted by alternative imaging and biopsy. We hypothesize that these false positive results were due to zoledronic acid inhibiting the cycle of tumor cell proliferation and bone resorption causing bony infarcts in a tumor dependent pathway that increases osteoblast activity. We hope that awareness of this rare phenomenon will encourage practitioners to prove bone metastasis in primary bone cancers by biopsy, or alternative imaging before concluding current therapy has failed.

Keywords: Zoledronic Acid; False positive Metastasis; bone cancer.

Introduction

Zoledronic acid (ZA) was approved for use in the United States in 2001, and is listed an "essential medicine" by the World Health Organization [1]. ZA is a nitrogen containing bisphosphonate that inhibits osteoclast function and prevents bone reabsorption. It has also been found to induce apoptosis of hematopoietic tumor cells by interfering with GTP-binding proteins which disrupts prenylation and leads to apoptosis [2,3].

ZA is used to treat hypercalcemia, osteoporosis and bone damage caused by cancer metastasis. In cancer patients with bone metastasis, it can decrease pain and occasionally induce tumor shrinkage [4]. For primary bone tumors, such as osteosarcoma (OST) and Ewing sarcoma (EWS), ZA has been trialed as part of a combination chemotherapy strategy in high-risk patients [5].

ZA acid can also induce abnormal bone remodeling [6-13]. Case reports, such as those from Van Poznek et al., have revealed a common bone remodeling induced by ZA, osteonecrosis of the jaw (ONJ) [6]. In a recent study of 3,491 patients taking ZA for treatment of bone metastases 2.8% of patients had ONJ by their third year of treatment. Although bone modifying agents like ZA were previously known to induce ONJ, recent findings have shown occurrences in the long bones of the lower limb [7,8].

We describe three patients with primary bone tumors on ZA who had imaging suggestive of relapse with new bony metastasis, that was contradicted by alternative modality imaging and then, by biopsy, found to be non-malignant. We hypothesize that these false positive results were due to ZA inhibiting the cycle of tumor cell proliferation and bone resorption - a tumor dependent pathway that increases osteoblast activity which could induce non-malignant bone growths.

Methods

We reviewed The National Library of Medicine, PubMed, Google Scholar, and Northwestern University's Galter Health Sciences Library Data Base. We search these key words: "zoledronic acid," "bone metastasis," "zoledronic acid and osteonecrosis," "bisphosphonate side effects," "zoledronic acid false positives," "bone modifying agent false positive," and "bone scan false positive." This search was limited to the English language.

Results

There were no reports of bony metastasis as a false positive result in a patient with primary bone cancer taking a bone modifying agent. Although most reviews described ONJ, none discussed ZA-induced osteonecrosis or other bones [10-13]. After getting approval from the IRB and consent from the patients, we report our experience with 3 patients who had presumed bony metastasis that proved to be false-positives.

Case Reports

Case #1: A 22-year-old female with multiply relapsed primary metastatic OST, on salvage chemotherapy (ifosfamide /etoposide) and ZA (4mg IV monthly x 8 months) presented with a painless lesion of the right humerus detected on surveillance bone scan and seen clearly on MRI (Figure 1a, 1b), but not evident on PET (Figure 1c). Complete resection of the mass showed bone necrosis with no evidence of malignancy.

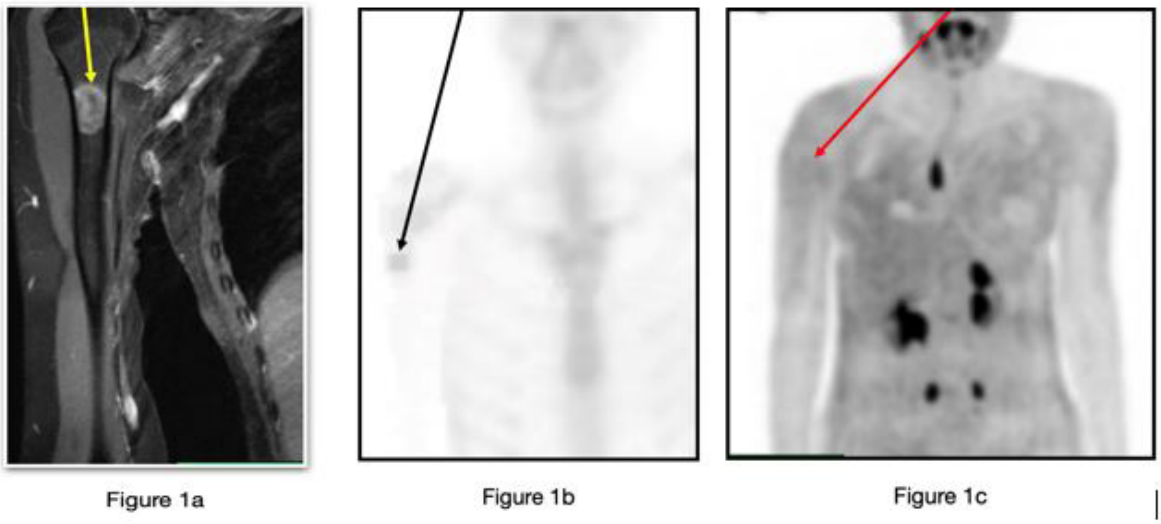

Figure 1: Multiply relapsed primary metastatic OST.

Case #2: A 19-year-old female with pelvic EWS and known bony metastasis, was treated with salvage chemotherapy (gemcitabine/ docetaxel) after relapse, that included ZA (4mg IV monthly x 14 months). She was found to have 2 asymptomatic skull lesions during a surveillance brain MRI (Figure 2).

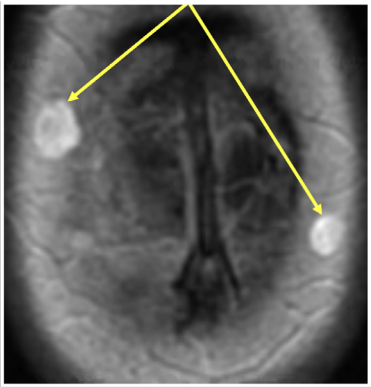

Figure 2b

Figure 2: pelvic EWS and known bony metastasis.

The lesions were not evident on bone scan. Complete resection of the masses showed bone necrosis with no evidence of malignancy.

Case #3: A 16-year-old with recurrent OST on salvage immunotherapy (nivolumab/lenvatinib) that included ZA (4mg IV monthly x 18), was found to have an asymptomatic, non-palpable, popliteal fossa lesion on surveillance bone scan (Figure 3), that was not evident on Xray.

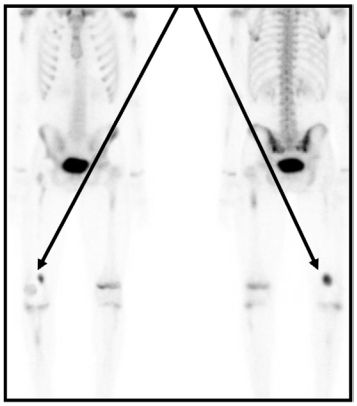

Figure 3

Figure 3: Recurrent OST on salvage immunotherapy.

At resection, the mass was composed of large osteoblasts, with no osteoclasts. There was no evidence of malignancy.

In all 3 cases there was lack of pain and lack of concordance between imaging modalities, with no malignant cells seen histologically.

In follow up: case # 1 died from a tumor-induced pulmonary hemorrhage one year later, without evidence of any new or suspicious bony metastasis while continuing the same therapy.

Case # 2 is alive and in remission 9 years later, off therapy.

Case # 3 is in a third remission of 19 months, still getting immunotherapy and ZA.

Discussion

Bone homeostasis is dependent on the osteoblast-osteoclast cycle. Osteoblasts and osteoclasts have been shown to have multiple cellular mechanisms of cell-to-cell communication, which keeps osteoblastic bone formation and osteoclastic bone reabsorption in balance. Central to this delicate balance is the receptor activator of NF-kB (RANK)/ receptor activator of NF-kB ligand (RANKL) pathway. Osteoblasts have RANKLs which bind to RANK receptors on osteoclasts to promote the differentiation and activation of osteoclasts. Metastatic cancers hijack this critical balance between osteoblasts and osteoclasts by over-expressing RANKLs, for example, OST cells express RANKLs, and EWS tumor-associated macrophages are RANKL-dependent. This over production of RANKLs accelerates the rate at which bone is reabsorbed by osteoclasts and induces osteolytic lesions that release various growth factors which promote tumor cell growth. ,

When ZA inhibits the formation of osteoclasts, the cycle of tumor cell proliferation and bone resorption is interrupted. This could induce osteonecrosis because old bone is not absorbed, and the vascular network is not maintained.

We hypothesize that the interruption of the tumor cell proliferation and bone resorption cycle is why ZA inhibits OST and EWS tumor cells, while the overabundance of osteoblasts enable non-malignant bone growths that mimic new metastases giving a false positive result on imaging.

Conclusion

When patients are treated with intensive ZA, a false positive result is possible due to inhibited osteoclast activity and increased osteoblast activity. Confirmatory imaging with alternative imaging modalities should be considered and, if possible, biopsy or resection before concluding there is a relapse or failure of systemic therapy.

Acknowledgments

We dedicate this work, in loving memory of Patient #1, KR.

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