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Normalization of Prostate-Specific Antigen and Reduction of Clinical Metastasis Following Zoledronic Acid Treatment in Castrate-Resistant Prostate Cancer

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ABSTRACT

Once prostate cancer reaches a castrate-resistant state with bone metastases, the typical next step in treatment is chemotherapy using agents of the taxoid family. In addition, in documented bony metastases, the biphosphonate zoledronic acid is used to prevent incidence of skeletal events. Zoledronic acid is also used to control bony pain and to increase bone mineral density. The patient in this case report had proven hormone-refractory, chemotherapy-naïve prostate cancer. This is the first documented instance of prostate-specific antigen (PSA) normalization and improvement on bone scan radionuclide imaging in a patient treated with zoledronic acid.

KEYWORDS: Castrate-resistant prostate cancer; Zoledronic acid; Metastasis; PSA

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CASE REPORT

A 77-year-old male was referred to the authors' institution for an elevated prostate-specific antigen (PSA) of 211 ng/mL. His past medical history included hypertension and gout. His only clinical sign was moderate lower urinary tract symptoms; he denied any pain or constitutional symptoms.

Evaluation

The patient's physical examination revealed a rock-hard prostate extending to the pelvic side-wall, reflecting a clinical stage T4 malignancy. His post-void residual was 80 cc. A transrectal ultrasound (TRUS) and prostatic biopsies were arranged. They revealed prostatic adenocarcinoma with a Gleason score of 9 (4+5), involving 5 out of 6 cores. The highest percentage of the tissue core involved was 50% (Figure 1). A staging CT of the abdomen and pelvis showed multiple para-aortic lymphadenopathy. Bilateral internal and external iliac and right common iliac lymphadenopathies were also observed. A bone scan revealed abnormal uptake in the lumbar spine, pelvis, rib cage, scapulae, manubrium, and right clavicle, suggestive of diffuse metastatic disease (Figure 2a).

Management and Follow-up

Based on the extent of the disease (clinical stage T4-N3-M1), the patient was started on combined androgen-deprivation therapy with goserelin and bicalutamide, along with oral vitamin D and calcium supplements. His PSA subsequently dropped to 1.31 ng/mL with a castrate testosterone level of 0.4 nmol/L. However, on subsequent blood draws his PSA gradually increased to a peak of 19.74 ng/mL, 10 months after initiation of androgen ablation. His serum testosterone level remained castrate and he continued to be asymptomatic. A follow-up bone scan revealed worsening abnormal uptake in the left sacroiliac joint, left hemipelvis, and right ilium, with stable disease elsewhere. Bicalutamide was discontinued. Four months later, the PSA remained at 18 ng/mL, thereby failing antiandrogen withdrawal. The patient was subsequently

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Figure 1. Fused and poorly defined glands with occasional lumina, alternating with solid sheets of malignant cells. The overall Gleason score was 4+5=9 (hematoxylin-eosin stain, original magnification 400x).

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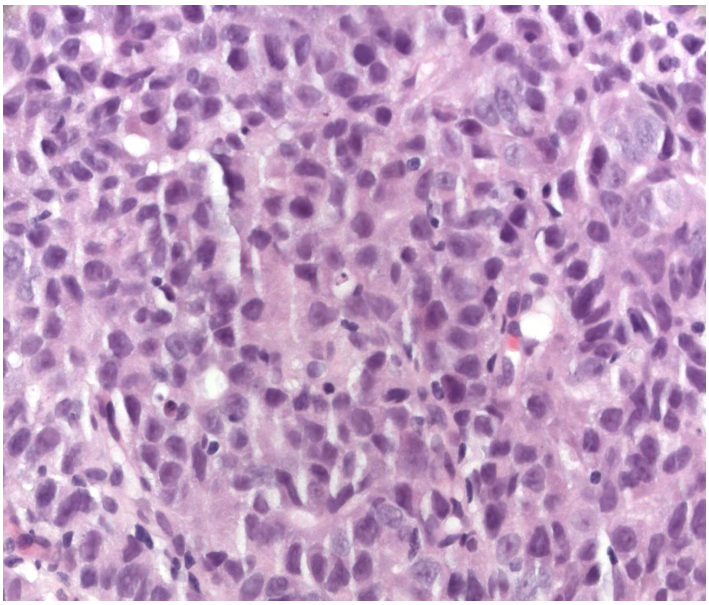

started on zoledronic acid, dosed at 3.3 mg IV every 4 weeks due to a reduced creatinine clearance. After initiation of this regimen, the PSA began to decrease to 2.5 ng/mL at 4 months and to a nadir of < 0.4 ng/mL (Figure 3). These values persisted over 23 months, to the present. He remains asymptomatic, and a second follow-up bone scan revealed a decrease in the abnormal uptake noted previously (Figure 2b).

DISCUSSION

Androgen deprivation therapy (ADT) is considered the cornerstone of locally advanced prostate cancer [1]. However, when the disease becomes castrate-resistant with bone metastases, options for treatment include chemotherapy with docetaxel-based regimens for prolongation of life, control of pain, and improvement in quality of life [2].

Zoledronic acid is a bisphosphonate that functions by inhibiting the bone resorption effects of osteoclasts [3]. The resulting reduction in the percentage of patients with a skeletal related event (SRE) has been well documented. SRE is defined as pathologic bone fracture, spinal cord compression, surgery or radiation therapy to bone, or change in antineoplastic therapy for bone pain. Zoledronic acid also prolongs the median time to the first SRE, reduces the annual incidence of SREs, reduces the overall risk of SRE [4], and improves pain scores [5] as well as bone mineral density [6] in patients with bone metastasis due to castrate-resistant prostate cancer. It can be used alone or in combination with either ADT or chemotherapeutic regimens. It has been shown to have a potentially additive and/or synergistic effect when used with docetaxel [7,8]. Furthermore, in a preclinical study, Morgan and colleagues [8] noted that "in patients with bone metastases due to castrate-resistant prostate cancer, who are not fit enough for systemic chemotherapy, single agent zoledronic acid may have a direct effect on viability of prostate cancer epithelial cells (p 669)."

Zoledronic acid has been shown to have several antitumor effects in the preclinical setting, including inhibiting angiogenesis [9], an important factor in cancer growth and progression. This mechanism is thought to be related to inhibition of endothelial progenitor cell (EPC) differentiation, and to induction of apoptosis in both endothelial progenitor and endothelial cells. These actions potentially affect both angiogenesis (growth of new blood vessels from preexisting ones) as well as vasculogenesis (creation of new vessels from EPCs derived from bone marrow). A second effect of zoledronic acid is specific to prostate cancer. Coxon et al [10] found that zoledronic acid inhibits the growth, proliferation, and promotion of apoptosis in prostate cancer cell lines *in vitro*. These authors demonstrated a dose-dependent effect of apoptosis induction on prostate cancer cells by zoledronic acid. The effect was abolished by the addition of a broad-spectrum inhibitor of caspase, an important enzyme in the apoptosis pathway. Furthermore, zoledronic acid inhibited cellular adhesion to mineralized matrix.

This is the first known case report of PSA normalization and improvement of bony metastases in a patient with castrate-resistant metastatic prostate cancer treated with zoledronic acid. This case reflects the first clinical documentation of the aforementioned *in vitro* benefits of zoledronic acid use. In addition to the known benefits of zoledronic acid in symptom and quality of life control in metastatic prostate cancer, this case shows that use of this bisphosphonate may have clinical gain for cancer control. These gains are manifested in the typical ways of monitoring the extent of metastatic disease, namely PSA and clinical disease progression on bone scan.

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Figure 2a. Radionuclide Bone Scintigraphy Before Initiation of Zoledronic Acid.

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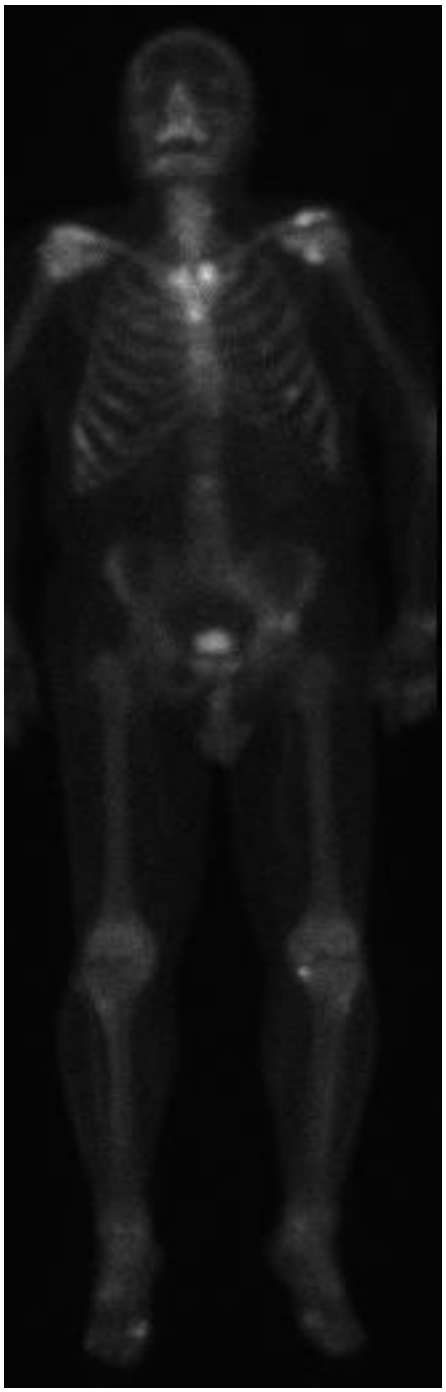

Figure 2b. Radionuclide Bone Scintigraphy 6 Months After Initiation of Zoledronic Acid.

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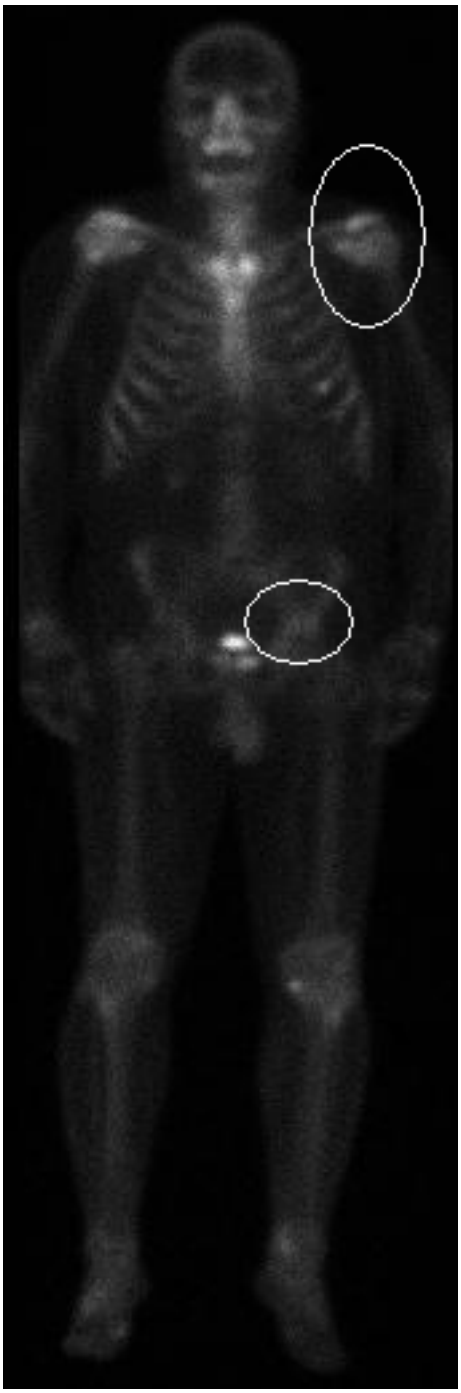

Sample areas of significant improvement are marked.

Figure 3. Prostate-Specific Antigen (PSA) Trend.
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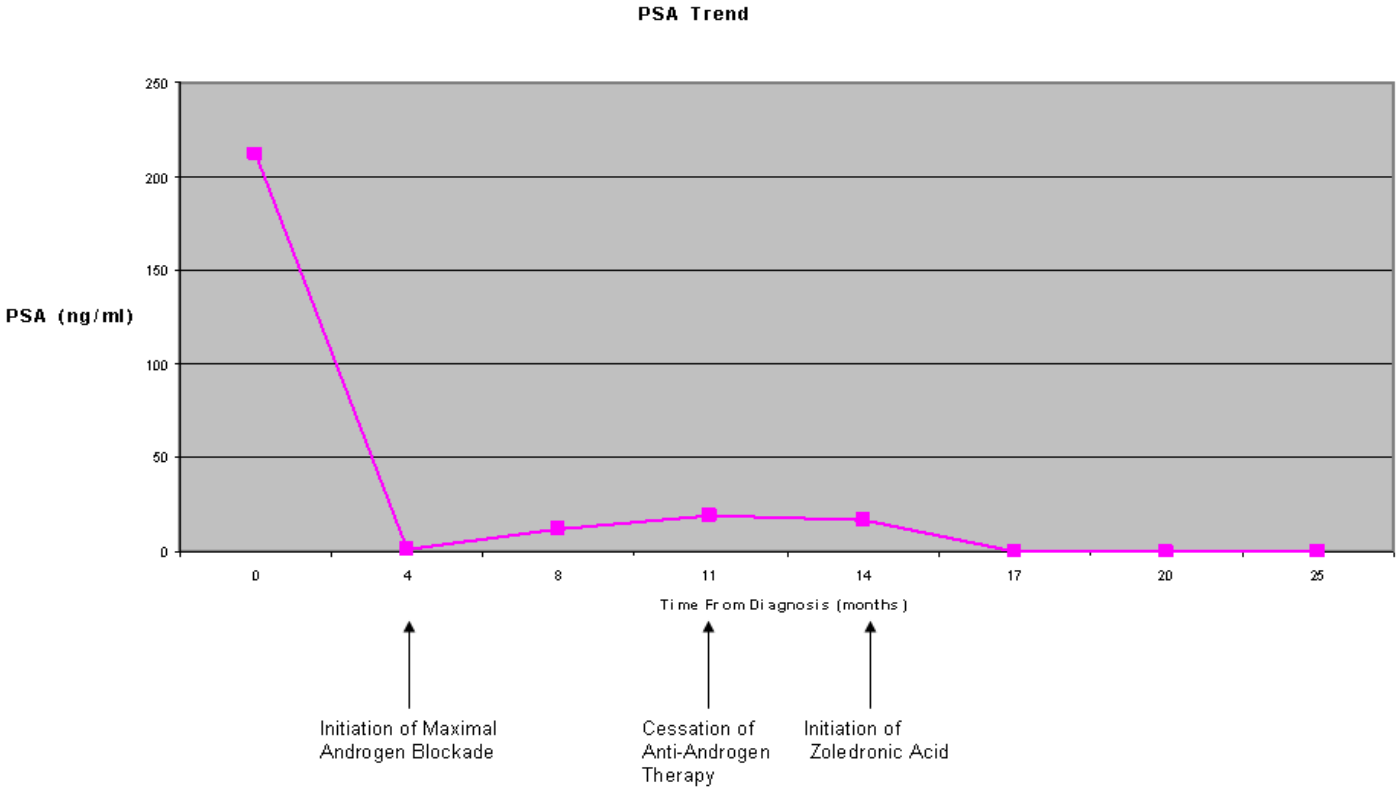

REFERENCES

[1] Zincke H, Oesterling JE, Blute ML, Bergstralh EJ, Myers RP, Barrett DM. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. *J Urol*. 1994;152(5 Pt 2):1850-1857.

[2] Mike S, Harrison C, Coles B, Staffurth J, Wilt TJ, Mason MD. Chemotherapy for hormone-refractory prostate cancer. *Cochrane Database Syst Rev.* 2006;(4):CD005247.

[3] Dhillon S, Lyseng-Williamson KA. Zoledronic acid: a review of its use in the management of bone metastases of malignancy. *Drugs*. 2008;68(4):507-534.

[4] Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. *Clin Prostate Cancer.* 2005;4(1):31-37.

[5] Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94(19):1458-1468.

[6] Saad F, McKiernan J, Eastham J. Rationale for zoledronic acid therapy in men with hormone-sensitive prostate cancer with or without bone metastasis. *Urol Oncol.* 2006;24(1):4-12.

[7] Ullén A, Lennartsson L, Harmenberg U, et al. Additive/synergistic antitumoral effects on prostate cancer cells in vitro following treatment with a combination of docetaxel and zoledronic acid. *Acta Oncol*. 2005;44(6):644-650.

[8] Morgan C, Lewis PD, Jones RM, Bertelli G, Thomas GA, Leonard RC. The in vitro anti-tumour activity of zoledronic acid and docetaxel at clinically achievable concentrations in prostate cancer. *Acta Oncol*. 2007;46(5):669-677.

[9] Yamada J, Tsuno NH, Kitayama J, et al. Anti-angiogenic property of zoledronic acid by inhibition of endothelial progenitor cell differentiation. *J Surg Res*. 2009;151(1):115-120.

[10] Coxon JP, Oades GM, Kirby RS, Colston KW. Zoledronic acid induces apoptosis and inhibits adhesion to mineralized matrix in prostate cancer cells via inhibition of protein prenylation. *BJU Int*. 2004;94(1):164-170.