

Oncology

Histopathology of castration-resistant prostate cancer confirms changes in bone metastasis during radium-223 treatment: A case report

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ABSTRACT

Radium-223 is used for treating castration-resistant prostate cancer with bone metastases. Here, we report the case of a 76-year-old man diagnosed with castration-resistant prostate cancer with bone metastases who was started on radium-223. Although the patient ultimately died from causes unrelated to the treatment before starting the third treatment course, we observed that radium-223 was more effective in areas closer to the bone cortex than in deeper tumor regions. Through histopathological analysis, we provide important mechanistic insights on the therapeutic effect of radium-223 in human prostate cancer bone metastases.

Introduction

Radium-223 (Ra-223) increases overall survival (OS) in castration-resistant prostate cancer (CRPC) patients with bone metastases. The therapeutic effect of Ra-223 on bone tumors has been reported *in vitro*.¹ However, no study has assessed the histopathological changes of bone metastases during or after Ra-223 treatment in humans. We report the case of a patient who received Ra-223 and had visible changes in bone metastases, confirmed histopathologically at autopsy.

Case presentation

A 76-year-old man with a medical history of chronic heart failure and arteriosclerosis obliterans but no special notes on family history or allergies, was treated with combined androgen blockade (CAB) after being diagnosed with prostate cancer; however, he developed CRPC 2 years after the treatment. He was then treated with estramustine, but the treatment was discontinued due to the exacerbation of heart failure. Since then, he had stopped visiting the Urology Department.

Two years after the discontinuation of treatment, he was admitted to the Cardiology Department because of obstructive arteriosclerosis of the lower limbs. His prostate-specific antigen (PSA) and alkaline phosphatase (ALP) levels were 36.2 ng/ml and 537 U/L, respectively, and he was

referred to the Urology Department. Presence of a tumor was confirmed by computed tomography and bone scintigraphy; he then resumed treatment. Bone metastases were visible in the right seventh rib, third lumbar vertebrae, and right ilium, without lymph node or visceral metastases (Tx N0 M1b, according to the TNM Classification of Malignant Tumors). Because the patient refused hormonal therapy and owing to the previously observed severe side effects of estramustine, we resumed CAB with degarelix and bicalutamide. Five months later, PSA and ALP levels decreased to 0.705 ng/ml and 224 U/L, respectively. Denosumab was administered after a tooth extraction performed because of tooth decay, which occurred during Ra-223 administration. Denosumab was administered once every 3 months, for a total of 3 times until the end of treatment. During the administration, the ALP value decreased slightly, but the PSA value continued to increase (Fig. 1).

Monthly Ra-223 treatment was initiated and no side effects were observed. Before the third dose, the patient was admitted to the Cardiovascular Department with heart failure symptoms. Despite planning to resume Ra-223 therapy once his general condition improved, the patient returned to hospital on the day of discharge (upon improvement of heart failure symptoms) with acute abdomen. Shortly after, he died. A pathological autopsy revealed that he had died of ischemic enteritis resulting in sepsis.

Histopathological examination revealed fibrotic tissue in the

Abbreviations: ALP, alkaline phosphatase; CAB, combined androgen blockade; CRPC, castration-resistant prostate cancer; OS, overall survival; Ra-223, radium-223; PSA, prostate-specific antigen; RANKL, receptor activator of nuclear factor- κ B ligand; SRE, skeletal related event.

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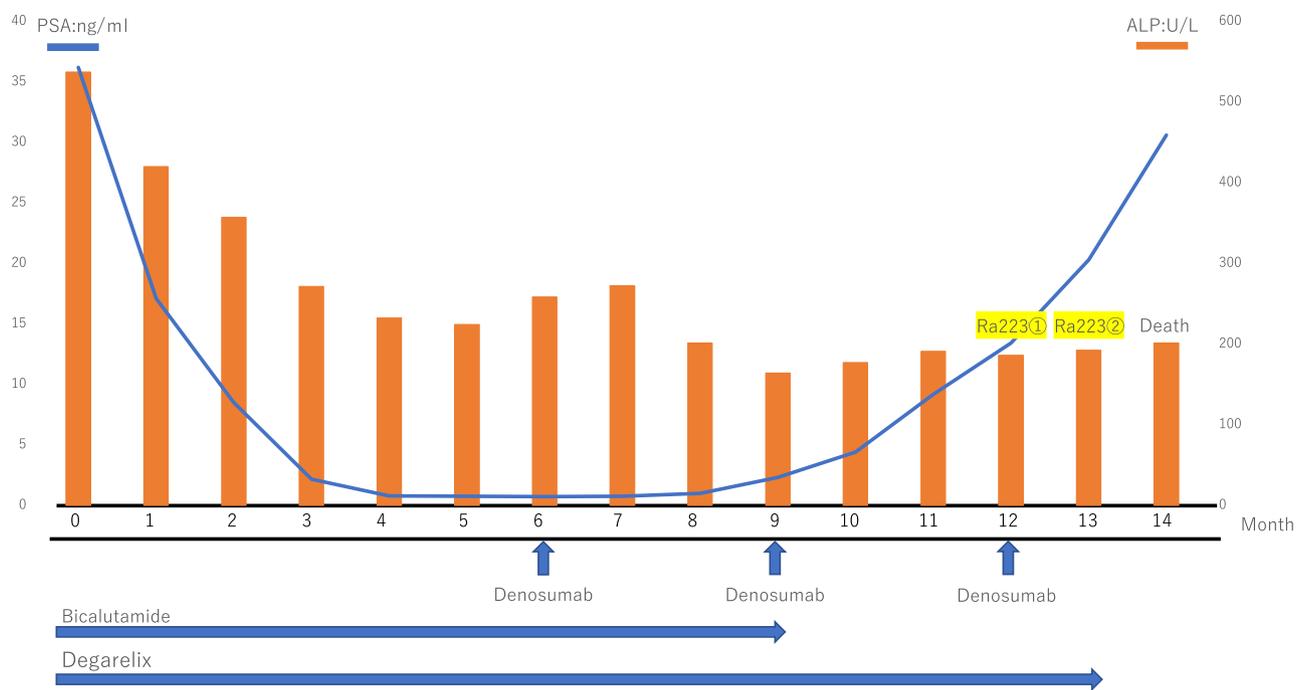


Fig. 1. Treatment of prostate cancer from diagnosis to death and changes in PSA and ALP values.

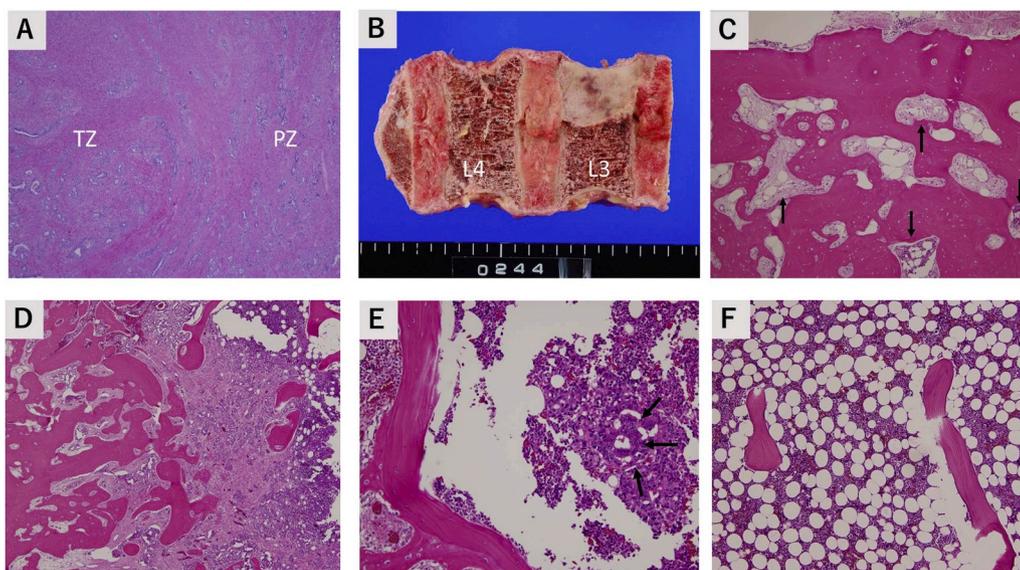


Fig. 2. Histopathological examination revealed fibrotic tissue in the prostate, which was suspected to be necrotic, but no viable tumor cells were detected. **A)** Macroscopic bone examination showed white-toned areas of osteosclerotic metastases on the left lateral side of the third lumbar vertebrae. **B)** Histological evaluation of bone tissue. **C)** Osteosclerotic changes are apparent near the bone cortex. Fibrous degenerative cells are indicated by an arrow pointing up, and inactive degenerative tumor cells are indicated by an arrow pointing down. **D)** Viable tumor cells are enriched in the deeper regions of the tumor (right side). **E)** Viable tumor and hematopoietic cells (indicated by arrows). **F)** Bone marrow tissue apparently unaffected by Ra-223.

prostate (Fig. 2A), which was suspected to be necrotic, but no viable tumor cells were detected. Macroscopic bone examination showed white-toned areas of osteosclerotic metastases on the left lateral side of the third lumbar vertebrae (Fig. 2B). Histopathology revealed fibrous tissue and inactive degenerative cells near the bone cortex in the metastatic region (Fig. 2C). However, closer to the trabecular area, we observed an increased proportion of viable tumor cells (Fig. 2D), which were found in close proximity to hematopoietic cells (Fig. 2E). No cytopathic effects were observed in normal bone marrow specimens (Fig. 2F).

Discussion

We report the case of a CRPC patient who underwent two doses of Ra223 treatment before dying of ischemic enteritis resulting in sepsis.

Inactive tumor cells were observed in the bone cortex but not in the trabecular area, suggesting that Ra-223 had a cytotoxic effect more pronounced in superficial areas of the tumor.

A study in mice with prostate cancer bone metastases showed that active bone remodeling microenvironments near bone metastases were the major site of Ra-223 accumulation.¹ According to the pathological study on bone metastasis of human prostate cancer subjected to CAB therapy,² the bone metastasis showed not only an increase in the number of osteoblasts in the prostate cancer cells and the bones responding to the prostate cancer cells but also a large amount of osteoid and osteoclasts. They also showed high bone turnover. Histopathologically, osteogenic tissues in bone metastatic lesions exhibit a cord-like structure. As a result, the short-range α radiation emitted by Ra-223 deposited in osteoblasts exerts antitumor effects across a wide area by irradiating tumor cell cords.³ We observed tumor cell degeneration in

osteogenic tissues adjacent to the bone cortex. However, this decreased with tumor depth, with a higher number of viable tumor cells present in deeper areas of the tumor. McKay reported prolongation of OS in the 5–6 Ra-223 dose group compared to the 1–4 dose group.⁴ In our case, Ra-223 was given only twice. Therefore, there is the possibility that a sufficient therapeutic effect could not be obtained due to the small number of doses.

The therapeutic effect of Ra-223 has been suggested even in cases where bisphosphonate treatment is resistant to bone metastatic lesions. On the other hand, denosumab not only acts to prevent skeletal-related events (SRE) in patients with bone metastasis by suppressing the receptor activator of nuclear factor κ B ligand (RANKL) signaling, but also, a direct and indirect antitumor effect has been suggested.⁵ In this case, denosumab was also used in combination with Ra-223. No report was found on the frequency of denosumab administration and the pathological changes to bone metastases; thus, a pathological study on denosumab treatment in this case was not possible. However, since the number of doses of denosumab itself is small in this case, it is unclear whether a direct pathological treatment effect on the bone metastases appears.

Since he died soon after starting the treatment; hence, long-term evaluation including imaging was not achieved. The change in bone lesions in the pathological results in this case was due to tumor degeneration and necrotic degeneration, which are considered to be therapeutic effects, on the bone surface part where the bone turnover is accelerated. This may be the expected therapeutic effect of Ra-223.

Conclusion

Histopathological analysis in this case showed that Ra-223 treatment

had a therapeutic effect on areas with increased bone turnover close to the bone cortex, despite other concomitant therapeutic factors. Results similar to those shown in the preclinical studies with mice were also observed in human pathological specimens.

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Declaration of competing interest

The authors declare that they have no competing interests.

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