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Case Report

Accurate Monitoring of the Response of Bone Metastases to Treatment in Patients with Prostate Cancer Using Choline PET/CT

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Abstract
We here report 2 cases of castration-resistant prostate cancer (CRPC) observed two times on ^{11}C-choline positron emission tomography computed tomography (PET/CT), which was useful to discriminate viable progressive osteoblastic bone metastasis from benign osteoblastic change induced by the treatment effect and to determine the viability of bone metastases, regardless of whether sclerosis was present or not. Because one case demonstrated disappearance of abnormal ^{11}C-choline uptake of osteoblastic metastatic lesions after abiraterone therapy and no new lesions at other sites, suggesting nonviable bone metastases, we can assume a complete metabolic response. Because the other case demonstrated a decrease in the existing, abnormal ^{11}C-choline uptake of osteoblastic metastatic lesions, but multiple new appearances of osteoblastic and nonosteoblastic lesions with abnormal ^{11}C-choline uptake after radium-223 therapy suggesting multiple viable bone metastases, we can assume progressive metabolic disease. ^{11}C-choline PET/CT could help in assessing the treatment response of bone metastases in patients with metastatic CRPC.

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Introduction

Prostate cancer ranks as the most common lethal malignancy diagnosed and the second leading cause of cancer mortality in Western countries. Although high response rates are achieved using androgen blockade as first-line therapy, most men progress toward hormone-refractory prostate cancer. Systemic chemotherapies have been shown to improve clinical outcome in hormone-refractory prostate cancer patients; however, they are not curative. Due to the high incidence of bone involvement in hormone-refractory prostate cancer, assessment of treatment response in prostate cancer metastatic to the bone remains a major clinical need.

Most advanced prostate cancer patients may harbor both viable osteoblastic bone metastases and treatment-induced sclerosis during the treatment course. Although computed tomography (CT) and bone scintigraphy are widely used to survey these calcified lesions, they are unable to discriminate between these two entities. On the other hand, choline positron emission tomography CT (PET/CT) can directly detect viable bone metastases in prostate cancer, regardless of whether sclerosis is present or not. Moreover, choline PET/CT can discriminate viable progressive osteoblastic bone metastasis from benign osteoblastic change induced by the treatment effect. Here we demonstrate 2 cases in which choline PET/CT was very useful to determine the viability of bone metastases and assess the treatment response of bone metastases in patients with prostate cancer.

Case Report

Case 1

Three years previously, a 64-year-old man with biopsy-proven prostate cancer (Gleason score 5 + 5), a serum prostate-specific antigen (PSA) level of 1.55 ng/mL (normal PSA value), and a clinical stage of T3bN1M1b underwent maximum androgen blockade therapy and castration as initial treatments. The PSA value increased and docetaxel was started with the diagnosis of castration-resistant prostate cancer (CRPC). However, in the latest half-year, the PSA value gradually increased by 0.006 ng/mL to 0.041 ng/mL, and the patient underwent a first ^{11}C-choline PET/CT examination to evaluate his current disease status. ^{11}C-choline PET/CT showed multiple osteoblastic lesions in the spine, pelvis, and ribs with no ^{11}C-choline uptake, reflecting treatment-induced sclerosis during the treatment course, as well as several instances of abnormal ^{11}C-choline uptake in the thoracic and lumbar spine sclerosis, suggesting viable tumors (Fig. 1a). New hormonal therapy (abiraterone) was started, which improved the PSA level to 0.008 ng/mL after 6 months. The second ^{11}C-choline PET/CT 6 months after starting abiraterone showed disappearance of the abnormal ^{11}C-choline uptake seen on the first ^{11}C-choline PET/CT and no new lesions at other sites, suggesting nonviable bone metastases (Fig. 1b). We can assume a complete metabolic response according to the two ^{11}C-choline PET/CT scans.

Case 2

Four years previously, a 69-year-old man with biopsy-proven prostate cancer (Gleason score 5 + 4), a serum PSA level of 207 ng/mL, and a clinical stage of T3aN2M1b underwent maximum androgen blockade therapy as initial treatment. The PSA value increased and CRPC was diagnosed, and a new hormonal therapy (in order: enzalutamide, abiraterone, and enzalutamide) was introduced. However, the PSA value gradually increased to 18.7 ng/mL and he underwent a first ^{11}C-choline PET/CT examination to evaluate his current disease status. ^{11}C-choline PET/CT showed multiple osteoblastic lesions and abnormal ^{11}C-choline uptake in the spine and pelvis, suggesting viable tumors (Fig. 2a). He received radium-223

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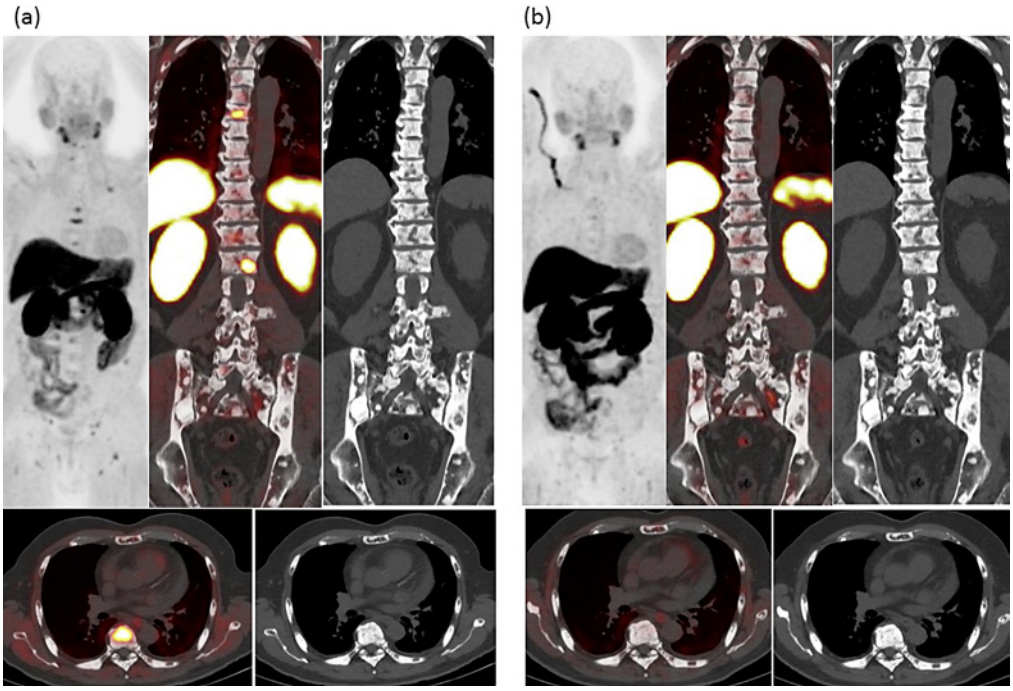

Fig. 1. A 64-year-old man with castration-resistant prostate cancer treated with abiraterone. **a** The first ^{11}C-choline PET/CT before abiraterone therapy showed multiple osteoblastic lesions in the spine, pelvis, and ribs with no ^{11}C-choline uptake, reflecting treatment-induced sclerosis during the treatment course, as well as several instances of abnormal ^{11}C-choline uptake in the thoracic and lumbar spine sclerosis, suggesting viable tumors. **b** The second ^{11}C-choline PET/CT 6 months after starting abiraterone showed disappearance of the abnormal ^{11}C-choline uptake seen on the first ^{11}C-choline PET/CT (**a**) and no new lesions at other sites, suggesting nonviable bone metastases. We can assume a complete metabolic response according to the two ^{11}C-choline PET/CT scans.

therapy for 6 months; however, the PSA value gradually increased to 160 ng/mL and he underwent a second ^{11}C-choline PET/CT examination to evaluate the effect of the radium-223 therapy. The second ^{11}C-choline PET/CT at the end of the radium-223 therapy showed a decrease in existing ^{11}C-choline uptake, but multiple new appearances of osteoblastic and nonosteoblastic lesions with abnormal ^{11}C-choline uptake in the spine, pelvis, ribs, and femur, suggesting multiple viable bone metastases (Fig. 2b). We can assume progressive metabolic disease according to the two ^{11}C-choline PET/CT scans.

Discussion

There are some problems in terms of evaluating bone lesions' characteristics in prostate cancer patients by using conventional serum and imaging evaluation techniques. For example, although PSA is the most widely used clinical biomarker of prostate cancer, a dissociation between PSA levels and state of disease may occur in CRPC patients [1]. CT and bone scintigraphy have been the most popular imaging methods for the evaluation of bone metastases in patients with prostate cancer. Bone metastases in prostate carcinoma are osteoblastic in about 80% of cases, mixed osteoblastic and osteolytic in 15% of cases, and purely osteolytic lesions occasionally (5%) [2], and bone scintigraphy relies on the detection of osteoblastic activity. However,

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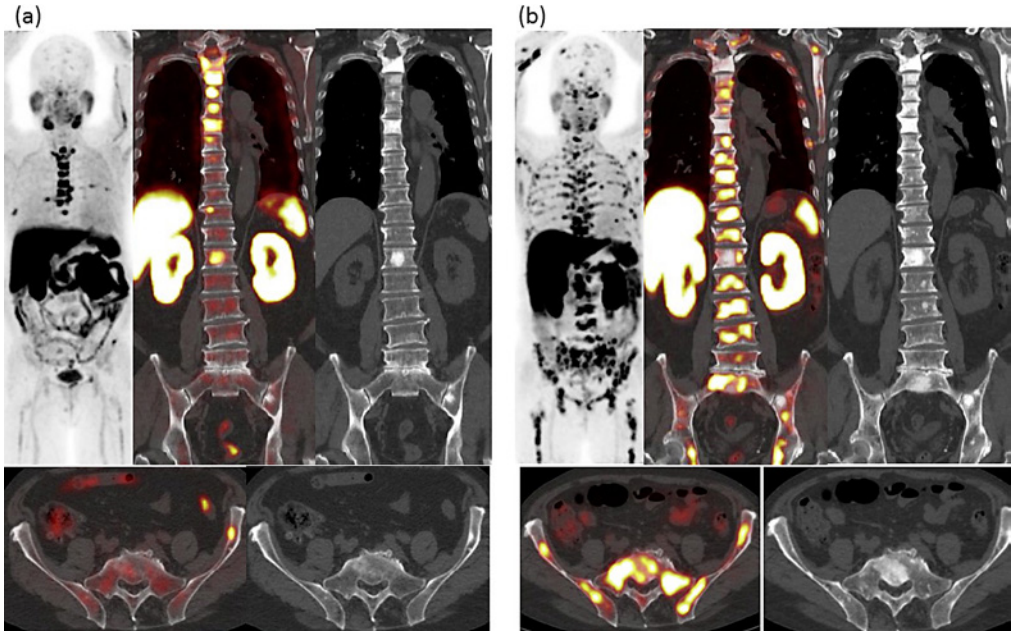

Fig. 2 . A 69-year-old man with castration-resistant prostate cancer was treated with radium-223 therapy. **a** The first ^{11}C-choline PET/CT showed multiple osteoblastic lesions and abnormal ^{11}C-choline uptake in the spine and pelvis, suggesting viable tumors. **b** The second ^{11}C-choline PET/CT at the end of the radium-223 therapy showed a decrease in existing ^{11}C-choline uptake, but multiple new appearances of osteoblastic and nonosteoblastic lesions with abnormal ^{11}C-choline uptake in the spine, pelvis, ribs, and femur, suggesting multiple viable bone metastases. We can assume progressive metabolic disease according to the two ^{11}C-choline PET/CT scans.

CT and bone scintigraphy have a limitation for evaluating metastases of prostate cancer, because both modalities are unable to discriminate viable osteoblastic bone metastases from treatment-induced sclerosis during the treatment course. The Response Evaluation Criteria in Solid Tumors (RECIST) regard bone scintigraphy as insufficient for an evaluation of tumor activity of bone metastases, and bone disease is judged as "nonmeasureable" by RECIST [3].

On the other hand, the European Organization for Research and Treatment of Cancer imaging group has positioned PET/CT using ^{11}C-choline or ^{18}C-fluorocholine as a potential first choice for monitoring the response of bone metastases to treatment in patients with prostate cancer [4]. As was clarified in our case series, choline PET/CT can determine the viability of bone metastases, regardless of whether sclerosis is present or not, and discriminate viable progressive osteoblastic bone metastasis from benign osteoblastic change induced by the treatment effect. In recent years, whole-body diffusion-weighted magnetic resonance imaging [4, 5] and ^{68}Ga prostate-specific membrane antigen PET/CT [6] have emerged as new imaging modalities for monitoring the response of bone metastases to treatment in patients with prostate cancer.

Conclusions

Choline PET/CT is very useful to discriminate viable progressive osteoblastic bone metastasis from benign osteoblastic change induced by a treatment effect and to determine the viability of bone metastases, regardless of whether sclerosis is present or not. Choline

PET/CT could assess the treatment response of bone metastases and enable us to design optimal treatment strategies for patients with metastatic CRPC.

Statement of Ethics

This report complies with the guidelines for human studies and includes evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Concept and design: K.K., S.Y., and K.Y.; acquisition of data: S.Y., M.F., Y.K., Y.Y., S.N., K.S., T.H., M.T., and A.K.; drafting of the manuscript: K.K.; critical revision of the manuscript for important intellectual content: S.Y., A.K., and K.Y. All authors approved the final version of the manuscript.

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