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## Bone flare after initiation of novel hormonal therapy in patients with metastatic hormone-sensitive prostate cancer: A case report

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### Abstract

#### BACKGROUND

The 2020 European Association of Urology prostate cancer guidelines recommend androgen deprivation therapy (ADT) in combination with apalutamide and enzalutamide, a new generation of androgen receptor antagonists, as first-line therapy. A decrease in prostate-specific antigen (PSA) levels may occur in the early stages of novel hormonal therapy; however, radionuclide bone imaging may suggest disease progression. During follow-up, PSA, radionuclide bone imaging, and prostate-specific membrane antigen (PSMA) positron emission tomography - computed tomography (PET-CT) are needed for systematic evaluation.

#### CASE SUMMARY

We admitted a 56-year-old male patient with metastatic hormone-sensitive prostate cancer. Initial radionuclide bone imaging, magnetic resonance imaging (MRI), and PSMA PET-CT showed prostate cancer with multiple bone metastases. Ultrasound-guided needle biopsy of the prostate revealed a poorly differentiated adenocarcinoma of the prostate with a Gleason score: 5+4 = 9. The final diagnosis was a prostate adenocarcinoma (T<sub>4</sub>N<sub>1</sub>M<sub>1</sub>). ADT with novel hormonal therapy (gosereline sustained-release implant 3.6 mg monthly and apalutamide 240 mg daily) was commenced. Three months later, radionuclide bone imaging and MRI revealed advanced bone metastasis. However, PSMA PET-CT examination showed a significant reduction in PSMA aggregation on the bone, indicating improved bone metastases. Considering that progressive decrease in the presenting lumbar pain, treatment strategies were considered to be effective.

#### CONCLUSION

ADT using novel hormonal therapy is effective for treating patients with prostate adenocarcinoma. Careful evaluation must precede treatment plan changes.

**Key Words:** Bone flare; Novel hormonal therapy; Metastatic hormone-sensitive prostate cancer; Apalutamide; Case report

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**Core Tip:** In 2018, prostate cancer was ranked as the fifth leading cause of cancer-related deaths in men, worldwide. Some of such cases are metastatic hormone-sensitive prostate cancers (mHSPC) and Apalutamide has been shown to improve survival in such patients. However, a “bone-flare” phenomenon may occur during management with apalutamide. We describe a case of mHSPC with this phenomenon after apalutamide and androgen deprivation therapy, and thus demonstrate the importance of multiple bone imaging modalities, radionuclide bone imaging, magnetic resonance imaging, prostate-specific antigen, prostate-specific membrane antigen positron emission tomography – computed tomography, in determining the treatment course in such patients.

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## INTRODUCTION

Prostate cancer (PCa) is ranked as the second most common cancer and the fifth leading cause of cancer-related deaths in men worldwide in 2018[1]. Unfortunately, some patients develop metastatic castration-resistant prostate cancer (mCRPC), including metastatic hormone-sensitive prostate cancer (mHSPC). In recent years, studies have confirmed that apalutamide sustains a lower level of prostate-specific antigen (PSA) and improves the survival of patients with mHSPC. Several international guidelines recommend apalutamide as the standard treatment for mHSPC. During follow-up, PSA and radionuclide bone imaging are needed for systematic evaluation. Following the application of novel hormonal therapy, PSA was noted to decrease significantly in some patients after treatment. However, radionuclide bone imaging showed progression of bone metastases after 3 mo and with a gradual decrease noted during subsequent follow-up. Ryan *et al*[2] calls this phenomenon “bone flare”. In this study, we retrospectively analyzed the “bone flare” phenomenon during apalutamide treatment in a patient with mHSPC. General information, clinical symptoms, laboratory and imaging examination, treatment, and follow-up data were collected and analyzed. We also share our experience regarding treatment of a patient who had the “bone flare” phenomenon during apalutamide treatment, and provide a reference for its clinical application.

## CASE PRESENTATION

### Chief complaints

The patient suffer lumbar pain for 1 mo.

### History of present illness

On December 16, 2020, a 56-year-old man visited the outpatient clinic of the Department of Urology, Weifang People's Hospital, with a complaint of lumbar pain for 1 mo.

### History of past illness

The patient had no relevant history of past illnesses.

### Personal and family history

The patient has no relevant personal and family history.

### Physical examination

Digital rectal examination revealed a significantly enlarged, hard prostate with palpable non-tender nodules on the left side.

**Laboratory examinations**

Initial hormonal assay results were as follows: PSA > 100 ng/mL, ALP: 730 U/L. Ultrasound-guided needle biopsy of the prostate. Postoperative pathological results were as follows: poorly differentiated adenocarcinoma of the prostate, Gleason score: 5+4 = 9.

**Imaging examinations**

Magnetic resonance imaging (MRI) revealed a malignant mass in the peripheral zone of the prostate with multiple bone metastases. Radionuclide bone imaging revealed multiple bone metastases. Prostate-specific membrane antigen (PSMA) positron emission tomography – computed tomography (PET-CT) examination revealed PSMA aggregation in multiple bone sites.

**FINAL DIAGNOSIS**

Based on the results obtained from imaging and histopathology, the final diagnosis was prostate adenocarcinoma (T<sub>4</sub>N<sub>1</sub>M<sub>1</sub>).

**TREATMENT**

Androgen deprivation therapy (ADT) using novel hormonal therapy (goserelease sustained-release implant 3.6 mg monthly and apalutamide 240 mg/d) was initiated on December 24, 2020.

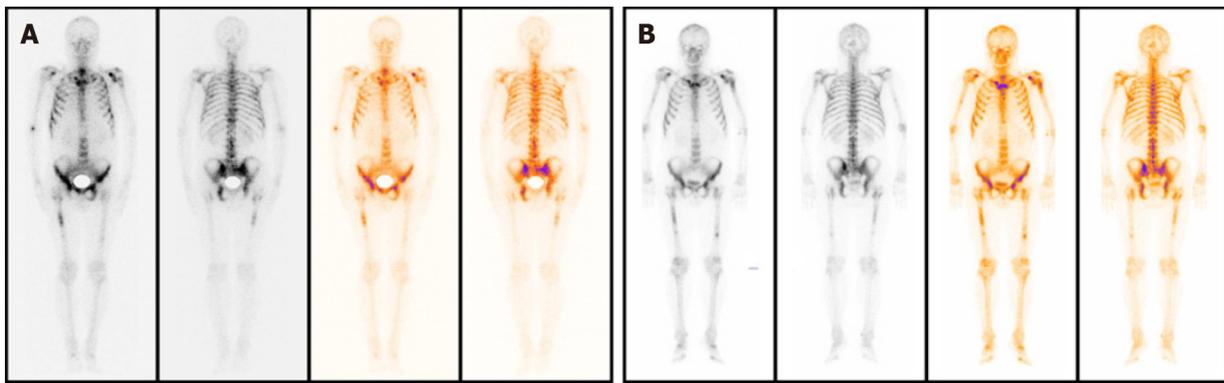
**OUTCOME AND FOLLOW-UP**

PSA levels and alkaline phosphatase levels were reviewed monthly, and imaging examinations were reviewed every three months. The PSA level decreased significantly during the treatment; however, three months later, radionuclide bone imaging and MRI indicated progression of the bone metastasis (Figure 1). Contrarily, PSMA PET-CT examination showed significantly decreased PSMA aggregation on the bone, indicating improved bone metastases (Figure 2). Considering that the lumbar pain, which he initially presented with, continued to decrease, the treatment strategies were considered to be effective. The original treatment strategies were continued for over 4 mo. The patient's PSA decreased to normal levels (Figure 3), and his clinical symptoms reduced significantly; therefore, treatment was continued.

**DISCUSSION**

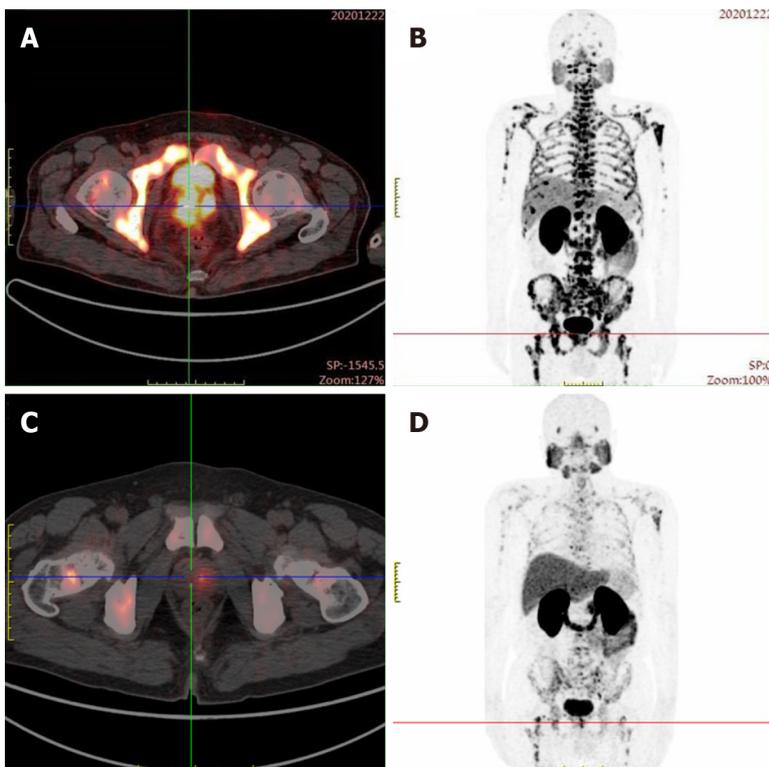
In most patients diagnosed with prostate cancer with distant metastases at the clinic, bone metastasis is the most common. Studies have shown that androgen receptors (AR) play an important role in the development of prostate cancer[3]. Therefore, ARs are an important target for the treatment of prostate cancer. However, with prolonged conventional AR-targeted drug therapy, patients with prostate cancer experience a reduction in therapeutic effect[4]. Presently, research and development of new AR-targeting drugs has become a hotspot in the field of prostate cancer treatment.

Apalutamide, an oral non-steroidal antiandrogen agent that binds directly to the ligand-binding domain of the androgen receptor and prevents androgen receptor translocation, DNA binding, and androgen receptor-mediated transcription[5], has shown good efficacy and safety in clinical practice. The 2020 EAU prostate cancer guidelines recommend ADT in combination with apalutamide and enzalutamide, a new generation of androgen receptor antagonists, as first-line therapy for metastatic prostate cancer. Ryan *et al*[2] reported that after abiraterone treatment for 3 mo, the PSA level decreased by more than 50%, but bone metastasis lesions increase. Furthermore, after 6 mo of continued treatment, bone scan revealed reduced or stable lesions, and this was termed the “bone flare” phenomenon. During treatment, the laboratory results of patients with the bone flare phenomenon showed no significant change in the alkaline phosphatase level, however, PSA level continued to decrease. Our case revealed that bone flare phenomenon also occurs with apalutamide therapy. Some studies have also shown that bone flare occurs in some breast cancer patients with bone metastasis after chemotherapy and other treatments, and is considered to be a sign of effective treatment of bone metastases. Cook *et al*[6] reported that of 22 patients with unequivocal skeletal metastases on baseline scan, flares occurred in 9 (41%). Out of 36 high-risk localized prostate cancer patients with normal pre-treatment bone scintigraphy, the scan became positive for metastases at 6 wk in 4 (11%). Furthermore, out of 41 patients, pre-treatment scintigraphic abnormalities of uncertain etiology and flares occurred in 8 patients (20%).



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Figure 1 Radionuclide bone imaging indicated progression on bone. A: Before the treatment; B: Three months later.



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Figure 2 Prostate-specific membrane antigen positron emission tomography – computed tomography examination showed abnormal prostate-specific membrane antigen aggregation was significantly reduced, and bone metastasis was significantly improved compared with baseline. A, B: Before the treatment; C, D: Three months later.

In the present study, the patient was diagnosed with mHSPC and bone metastasis. The initial treatment strategy was ADT and apalutamide. However, bone flares occurred 3 mo after treatment, and a bone scan showed metastatic progression. However, PSMA PET-CT examination showed that abnormal PSMA aggregation was significantly reduced, and bone metastasis was significantly improved compared to the baseline. Therefore, the temporary phenomenon of increased lesions in the bone scan was considered a bone flare. During treatment, the PSA level decreased significantly, and the alkaline phosphatase level did not change significantly. Vincenza *et al*[7] pointed out that therapy for metastatic disease may lead to healing and new bone formation, which causes an initial increase in tracer uptake (akin to callus formation). This deterioration, followed by subsequent improvement in the bone scan appearance after successful therapy, is defined as a flare response. Due to the shortcomings of the current assessment based on PSA and imaging examinations, more research results show that the changes in the number of circulating tumor cells in peripheral blood can be used as a new means of evaluating efficacy. If the treatment is effective, the number of circulating tumor cells will decline rapidly. The increase or decrease in the number of circulating tumor cells after treatment is also a

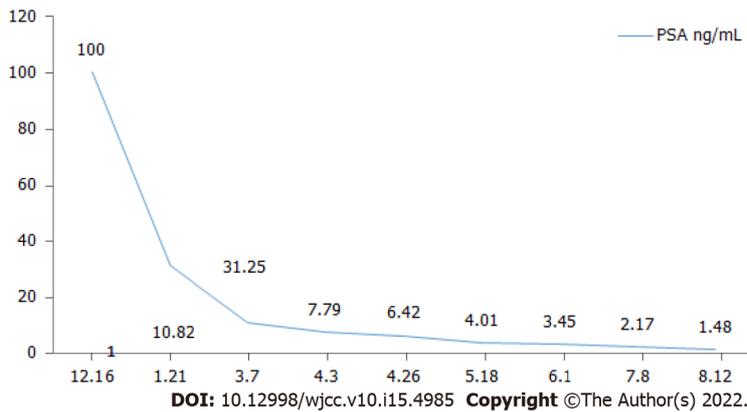


Figure 3 Prostate-specific antigen curve.

predictor of patient survival. The prognostic value is significantly better than PSA and imaging examination[8,9]. In the latest PCWG3 study, assessment of circulating tumor cell number was used as an important marker for disease evaluation and to assess drug efficacy[10].

Therefore, during the novel hormonal therapy in mHSPC patients with bone metastasis, it is important to identify whether the treatment is ineffective or whether the bone flare phenomenon is observed when bone scan indicates bone disease progression. This will determine the subsequent treatment strategy for patients. If PSA levels are not reduced after treatment and clinical symptoms worsen, the possibility of disease progression should be considered, and a new treatment strategy should be selected. Otherwise, bone flare should be considered if the PSA level decreases significantly after treatment, and the patient's clinical symptoms improve significantly. In this case, the original treatment was maintained with close follow-up. Bone scan showed increased metastases, but the PSA level decreased significantly. Following PSAM, PET-CT results showed significant improvement in bone metastasis, and the bone flare phenomenon was confirmed.

## CONCLUSION

When apalutamide therapy is used in the treatment of prostate cancer, an increase in metastatic bone lesions on radionuclide bone imaging and MRI; warrants the use of other examinations including PSA, PSMA PET-CT, to determine the efficacy of ongoing treatment, so as to determine the course of treatment for such patients.

## FOOTNOTES

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