CASE REPORT

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Abiraterone Acetate Plus Prednisone Induced Bilateral Avascular Necrosis of the Femoral Head

Serhat SEKMEK[1], Bülent ÖZKURT[2], Mirmehdi MEHTİYEV[1], Öznur BAL[1], Efnan ALGIN[1]

[1]Ankara Bilkent City Hospital, Clinic of Medical Oncology, Ankara, Türkiye
[2]Ankara Bilkent City Hospital, Clinic of Orthopaedics and Traumatology, Ankara, Türkiye

ABSTRACT

Abiraterone acetate (AA) is an inhibitor of cytochrome P450c17 that suppresses androgen synthesis from steroid precursors. Prednisone (P) is coadministered with AA to correct the glucocorticoid deficiency resulting from AA-induced alterations in steroid synthesis and to suppress excessive mineralocorticoid effects. We report bilateral avascular necrosis of the femoral head in a patient treated with AA+P; this condition is usually seen with long-term, high-dose glucocorticoid use. A 54-year-old male patient was diagnosed with castration-resistant metastatic prostatic adenocarcinoma (Gleason score 4+5). Following progression on androgen deprivation therapy+docetaxel, AA+P treatment was initiated. During this treatment period, the patient was in remission for thirty months; later, he developed bilateral avascular necrosis of the femoral heads and was referred to orthopaedics. Core decompression surgery was performed on both femoral necks due to avascular necrosis. Management and outcome: AA+P treatment was not discontinued because of the highly successful results in treating prostate cancer, and the patient remains in remission while continuing this treatment. AA+P is a treatment for prostate cancer that inhibits androgen synthesis. Although P is administered in low doses to prevent abiraterone-induced reductions in glucocorticoid levels, serious glucocorticoid side effects may, in rare cases, develop in these patients. To our knowledge, this is the first report of such a side effect in the literature.

Keywords: Abiraterone; avascular necrosis; prednisone; prostate cancer

INTRODUCTION

Prostate cancer is the second most common cancer and the fifth leading cause of cancer-related death among men worldwide.[1] The risk of prostate cancer increases with age; incidence exceeds 60% in men older than 65 years.[2]

Firstly, in the Cougar Oncology (COU)-abiraterone acetate (AA)-301 study, longer overall survival (OS) was observed with AA than with placebo in patients with castration-resistant prostate cancer who had previously received docetaxel treatment.[3] Later, in the COU-AA-302 study, AA was tested against placebo in chemotherapy-naive patients, and both progression-free survival and OS were superior to those with placebo.[4] In the LATITUDE and STAMPEDE studies, androgen deprivation therapy (ADT) with AA plus prednisone (P) (AA+P) resulted in longer OS than ADT with placebo in patients with high-risk metastatic hormone-sensitive prostate cancer.[5,6] Since the results of these studies were reported, the use of abiraterone in the treatment of castration-naive metastatic prostate cancer has become widespread.

AA is a selective and irreversible inhibitor of cytochrome P450c17 (17α-hydroxylase/C17,20-lyase), an enzyme required for androgen biosynthesis. This inhibits the synthesis of testosterone precursors such as dehydroepiandrosterone and androstenedione, as well as glucocorticoids, since this enzyme is also involved in their synthesis. As a result of relatively increased mineralocorticoid activity, side effects such as hypertension, hyperkalemia, and edema occur.[5] P is administered to correct the glucocorticoid deficiency resulting from abiraterone-induced changes in steroid synthesis and to suppress excessive mineralocorticoid effects.[7]

Correspondence: Serhat SEKMEK MD,
Ankara Bilkent City Hospital, Clinic of Medical Oncology, Ankara, Türkiye
E-mail: serhatsekmek@gmail.com
ORCID ID: orcid.org/0000-0003-4650-248X

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Since P is used in physiological doses to replace deficiencies, glucocorticoid-related side effects are not expected. This case report describes bilateral avascular necrosis of the femoral head —a condition usually seen with long-term, high-dose glucocorticoid use— in a patient treated with AA+P. Informed consent was obtained from the patient and the patient's family for publication of the case report.

CASE REPORT

A 54-year-old man with no prior medical history was admitted to the department of urology, presenting with intermittent haematuria and dysuria for approximately one year. In August 2020, the prostate-specific antigen (PSA) level was 10.57 ng/mL; a 12-quadrant prostate biopsy was performed, and Gleason 4+5 prostatic adenocarcinoma was diagnosed in all 12 quadrants. No visceral organ metastases were detected on the computed tomography (CT) scan for staging. Whole-body bone scintigraphy showed increased osteoblastic activity in the posterior aspect of the right ninth rib, suspicious for metastasis. Subsequently, prostate-specific membrane antigen (PSMA) positron emission tomography (PET)-CT revealed no bone metastases; however, the patient was referred to the oncology department due to diffuse involvement of the prostate gland and regional lymph nodes. Radiotherapy was considered inappropriate for the patient with diffuse lymph node involvement because of the high risk of toxicity. Treatment with ADT (leuprolide 225 mg every three months) plus docetaxel (75 mg/m^2 every three weeks) was then planned. After four cycles of docetaxel treatment, the patient's PSA decreased to 2.5 and testosterone level to; however, PSMA PET-CT revealed new bone metastasis in the seventh thoracic vertebra (T7) and new paraaortic and parailiac lymph nodes, findings that were not considered oligoprogression. Due to radiological progression, he was assessed as having castration-resistant metastatic prostate cancer. In February 2021, docetaxel was discontinued, and AA (four tablets of 250 mg daily) plus P (5 mg twice daily) treatment was initiated. The PSA level decreased to 0.1 ng/mL during AA+P+ADT treatment. In the first month of treatment, the patient experienced grade 1 elevations in liver function tests and grade 1 fatigue. These side effects sometimes improved during treatment and sometimes relapsed, but did not progress. PSMA PET-CT showed a near-complete response in the T7 lesion and a partial response in the lymph nodes; the current treatment was continued. He began complaining of severe bilateral hip pain in August 2023. When the patient's pain was evaluated using the visual analogue scale, he rated it 8 out of 10 (very severe). The patient reported that he had difficulty even performing his daily activities due to pain and that his quality of life was impaired. The patient did not require orthopaedic aids for ambulation. The patient was not taking any medications other than prostate cancer treatments when he experienced this pain. No increase in PSA levels was detected. Laboratory values showed normal calcium levels, and bone mineral density measurement showed no osteoporosis. The patient had an orthopaedic consultation, and magnetic resonance imaging of the hip revealed no findings compatible with metastasis but showed degenerative bone changes, millimetric bone infarcts, effusion, and areas of bone marrow edema compatible with bilateral femoral head avascular necrosis (Figures 1, 2). The patient was evaluated by the tumour board, which decided to perform orthopaedic surgery for avascular necrosis. Core-decompression surgery was performed on the left femoral neck in September 2023 and on the right femoral neck in December 2023. Pathology results did not show any findings compatible with malignancy. AA+P treatment was not discontinued due to the highly successful results obtained in the treatment of prostate cancer and the patient is still in remission under this treatment. The adverse event developed after the patient started abiraterone (2 points); no other cause that could have

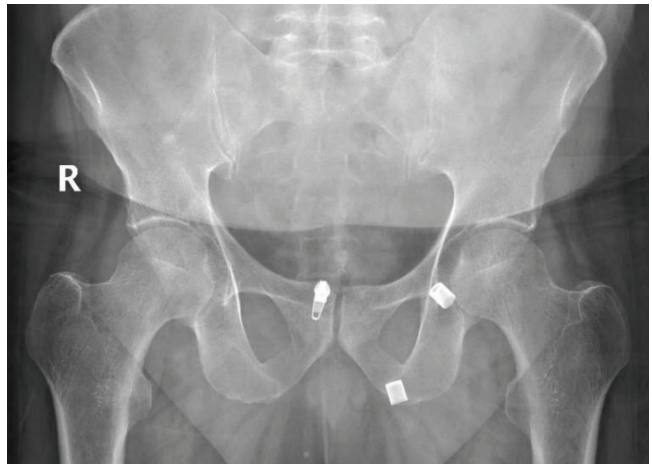

FIGURE 1: Pelvic X-ray of the patient.

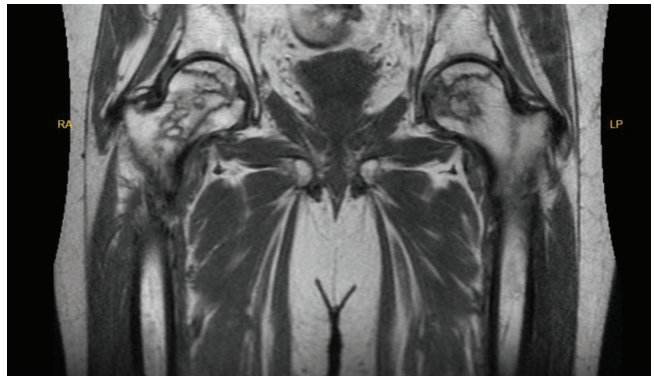

FIGURE 2: Pelvic magnetic resonance imaging of the patient.

led to this situation was identified (2 points); and the adverse event was objectively confirmed by imaging methods (1 point). The Naranjo Adverse Drug Reaction Probability scale score was calculated to be 5 in this case, indicating a probable association between this side effect and the drug (Figure 3). This side effect has not been reported to any local supervisory board or the pharmaceutical manufacturer.

DISCUSSION

AA is an androgen synthesis inhibitor used in the treatment of prostate cancer. In this case report, we describe the development of bilateral avascular necrosis of the femoral heads in a patient receiving abiraterone. To our knowledge, this is the first case in the literature of this association.

The most frequently observed side effects related to AA treatment are hypertension and hyperkalaemia. These side effects are due to abiraterone's inhibition of cytochrome P-450c17, which reduces both glucocorticoid and androgen synthesis, and to the consequent loss of negative feedback on adrenocorticotrophic hormone (ACTH), leading to increased ACTH secretion that stimulates mineralocorticoid synthesis in the adrenal glands. ACTH can be restored to its normal rhythm by physiological steroid replacement. This results in regularisation of mineralocorticoid synthesis and resolution of AA-related side effects.[8,9] To prevent these side effects related to the drug's mechanism of action, AA must be used in combination with physiological doses of cortisone.

Avascular necrosis of the femoral head may develop in patients receiving glucocorticoid therapy, depending on patients' comorbidities, the dose, and the duration of therapy. A meta-analysis showed that the risk of avascular necrosis increased by 3.6% per 10 mg/kg increase in glucocorticoid dose, particularly at doses higher than 20 mg/day.[10] In contrast, another study of 98,380 patients reported a 0.13% risk of avascular necrosis among patients receiving less than 15 mg of methylprednisolone daily.[11]

Patients using AA+P are not expected to experience side effects from physiological doses of glucocorticoids, which are

Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total Score:			

Naranjo Algorithm - ADR Probability Scale

Score	Interpretation of Scores
Total Score ≥9	**Definite**. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
Total Score 5 to 8	**Probable**. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible**. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful**. The reaction was likely related to factors other than a drug.

FIGURE 3: Narenjo adverse drug reaction probability scale.

administered to replace the deficiency. However, in our case, bilateral avascular necrosis of the femoral head developed in a patient receiving AA+P treatment, who required surgical intervention. Other possible etiologies of avascular necrosis include alcohol addiction, rheumatological diseases such as systemic lupus erythematosus, genetic diseases such as sickle cell anaemia, and trauma.[12-14] Since our patient did not have any of these causes, and avascular necrosis occurred following administration of AA+P, we consider that this side effect is related to AA+P treatment. To our knowledge, our case is the first reported in the literature on this subject.

The conditions caused by hypercortisolemia are well known, and reports of hypercortisolemia and hypercortisolemia-related serious side effects in patients receiving AA+P treatment are very rare in the literature. Given the mechanism of action, studies and case reports have investigated the efficacy of AA in adrenocortical cell culture models and in the treatment of Cushing's syndrome.[15,16]

CONCLUSION

AA+P is a treatment used in prostate cancer and inhibits androgen synthesis. Although P treatment is in low doses and is used to prevent abiraterone-induced low glucocorticoid levels, serious glucocorticoid side effects may develop in these patients, in rare cases. Therefore, patients receiving AA+P treatment should be cautious about possible side effects.

Ethics

Informed Consent: Informed consent was obtained from the patient and the patient's family for publication of the case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., B.Ö., Concept: S.S., Ö.B., E.A., Design: S.S., E.A., Data Collection or Processing: S.S., B.Ö., M.M., Ö.B., E.A., Analysis or Interpretation: S.S., M.M., Literature Search: S.S., E.A., Writing: S.S.

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