Case Report

Adrenal Insufficiency Induced by Continued Abiraterone Acetate Use in a Prostate Cancer Patient in Remission: The Dangers of Unmonitored Long-Term Therapy Without Corticosteroids

Ahmed S. Mohamed *, Ahmad R. Awwad , Angel Ann Chacko , Shraboni Dey , Brianna Braithwaite , Ruchi Bhuju , Sameh Elias

Posted Date: 19 February 2025

doi: 10.20944/preprints202502.1404.v1

Keywords: Abiraterone acetate; Adrenal insufficiency; prostate cancer; Mineralocorticoid excess syndrome; prednisolone; CYP17A1

 doi:10.20944/preprints202502.1404.v1

Case Report

Adrenal Insufficiency Induced by Continued Abiraterone Acetate Use in a Prostate Cancer Patient in Remission: The Dangers of Unmonitored Long-Term Therapy Without Corticosteroids

Ahmed S. Mohamed [1,*], Ahmad R. Awwad [1], Angel Ann Chacko [1], Shraboni Dey [1], Brianna Braithwaite [1], Ruchi Bhuju [1] and Sameh Elias [3]

[1] Department of internal medicine, Hackensack Meridien Health, Palisades medical center

[2] Transitional year program, Hackensack Meridien Health, Palisades medical Center

[3] Internal medicine program director, Hackensack Meridien Health, Palisades medical center

* Correspondence: ahmed.mohamed2@hmhn.org

Abstract: This case report presents a rare occurrence of adrenal insufficiency induced by Zytiga (abiraterone acetate) in a patient with high risk localized prostatic adenocarcinoma. Abiraterone acetate is a potent, selective and irreversible CYP17A1 inhibitor, and is commonly used in the treatment of prostate cancer, but it can cause various endocrine side effects, especially if not used concurrently with the appropriate treatment. The clinical implications of this adverse event and the management strategies are discussed here in this case report to raise awareness about this potential risk in patients with prostate cancer undergoing treatment with abiraterone acetate especially when used in an erroneous manner without monitoring.

Keywords: abiraterone acetate; adrenal insufficiency; prostate cancer; mineralocorticoid excess syndrome; prednisolone; CYP17A1

1. Introduction

Abiraterone acetate (Zytiga) is a 2nd generation (novel) antiandrogen that selectively and irreversibly inhibits the enzyme CYP17A1, which plays a key role in androgen biosynthesis inhibition in the testes, adrenal glands and the prostatic tissue. In metastatic settings, it is used with prednisone/prednisolone and androgen deprivation therapy (ADT) as a first-line treatment of high-volume disease metastatic castrate sensitive prostate cancer (mCSPC) as it showed improved overall survival (OS), and radiographic Progression-Free Survival (PFS) as compared to ADT alone [1,2]. An important mechanism androgen deprivation therapy fails to control tumor progression is that the tumor cells evade this by converting steroid precursors into androgens intracellularly. This mechanism promoted novel antiandrogen drugs, including abiraterone acetate to be used in the treatment of metastatic castrate- resistant prostate cancer (mCRPC) after progression on 1st line treatment (e.g. ADT+ Chemotherapy (Docetaxel) [3–5]. In the localized non-metastatic settings, long-term ADT in combination abiraterone acetate+ prednisone for 2 years with concurrent radiotherapy is the standard of treatment in high/very high-risk prostate cancer (>/=Grade 4/Gleason 8-10, PSA> 40 or >T3a) which showed improved OS and failure-free survival than ADT alone [1].

Through CYP17A1 inhibition However, abiraterone acetate can cause cortisol deficiency with a state of excess of mineralocorticoids in a similar manner to 17-alpha hydroxylase deficiency in congenital adrenal hyperplasia (CAH). To avoid the clinical manifestations of such disorders, patients are started on prednisone simultaneously to mitigate the potential occurrence of mineralocorticoid excess syndrome (MES) and adrenal insufficiency (AI). Due to its complex

 doi:10.20944/preprints202502.1404.v1

mechanism of action, there are no established criteria to diagnose or confirm MES or AI. Its mechanism of action can lead result in wide-range side effects, such as hypertension and hyperkalemia, which are implicative of MES. On the other hand, symptoms of adrenal insufficiency, most notably, fatigue can occur. Adrenal insufficiency is a rare, potentially serious and underrecognized complication in patients receiving abiraterone acetate therapy. It tends to occur more in periods of stress, when the lack of cortisol synthesis induced by abiraterone acetate overrides the MES state. Here, we describe a case of abiraterone acetate-induced adrenal insufficiency after having a thoracic spine fracture in a patient with localized, High-risk prostate cancer patient who despite achieving remission with ADT and abiraterone for 24 months, continued to take abiraterone acetate without prednisone and proper monitoring.

2. Case Presentation:

2.1. Patient Information

A 77-year-old male with a history of stage IIIC (cT2N0M0), high-risk prostate cancer (1ry Gleason score (4+5), stage IIIC) diagnosed in 2019, hypertension, Type II DM and dyslipidemia who presented with symptoms of Failure to thrive (FTT) with a main complaint of dysphagia to solid food associated with dyspepsia and severe fatigue. Patient started developing these symptoms after sustaining a fall on early October of 2024 that resulted in acute non-displaced, transverse fracture of T11 and T12 superior endplates. Ever since, the patient had been having generalized weakness and fatigue with no focal deficits. Patient denied sensory deficits, saddle anesthesia, bladder or bowel incontinence. Patient's dysphagia had also been worsening forcing him to eat thinner food, because he felt pain and sensation of the food getting stuck in his lower chest after he eats. He denied nausea, vomiting, diarrhea, fever, chills, cough, shortness of breath, hemoptysis or any other symptoms. Patient was admitted to the hospital prior to that encounter for the workup of the same symptoms. He underwent upper GI endoscopy which showed gastritis/erosions with duodenal clean-based ulcer and prominent ampulla. Biopsies were taken which came back negative for malignancy and positive for H pylori. He was discharged on triple therapy to present with worsening symptoms on the same day. Regarding his prostate cancer treatment, patient received concurrent external beam radiotherapy with long-term ADT (Lupron injection Q 3 months) in addition to abiraterone acetate and prednisolone, which should have ended in July 2022.

Patient's blood pressure on admission 95/60.

Lab findings:

CBC: WBCs: 3.51. Hgb: 11.1, Platelet count: 278

Chemistry: Glucose: 108, Na: 142, K: 4.2, Cl: 105, HCO3: 26, Elevated BUN: 31 and creatinine: 1.82, Mg: 1.5, Ca: 8.4, Albumin: 2.8, PO4: 2.6, ALT: 49, AST: 28, Alkaline phosphatase: 82, Lipase: elevated at 142, T PSA: <0.01.

CT Chest, abdomen and pelvis: Showed no evidence of metastatic disease and no evidence of acute pancreatitis.

Patient was admitted for further workup and management. After a very detailed medication reconciliation with the patient and the family, patient was found to have been intermittently on abiraterone acetate with days of him taking up to 12 pills a day (3000 mg) without prednisone, despite achieving remission after finishing two years of treatment and having undetectable PSA levels on follow ups.

The findings, combined with the patient's clinical presentation, were suggestive of a possible adrenal insufficiency, given the patient's recent fracture which might have put him under physiological stress in the setting of continued abiraterone acetate use without prednisone

2.2. Diagnostic Evaluation

Given the patient's symptoms and laboratory findings, the possibility of adrenal insufficiency induced by abiraterone acetate, especially with the erroneous intake without corticosteroids was

 doi:10.20944/preprints202502.1404.v1

considered. A morning cortisol level was obtained, which was markedly low (1.4 µg/dL, normal range 5-23 µg/dL), followed by failure to achieve peak cortisol secretion on Cosyntropin stimulation (30 minutes: 9.8 and 60 minutes:14.4) test confirmed the diagnosis of adrenal insufficiency.

2.3. Treatment and Management

We immediately discontinued abiraterone acetate and maintained the patient on intravenous fluids to correct his volume status. We added hydrocortisone (5 mg in the morning and 5 mg in the afternoon) to replace the deficient corticosteroid levels. The patient's blood pressure and symptoms of fatigue began to improve within 24–48 hours, and he was discharged with instructions to taper the hydrocortisone dose gradually over the next few weeks. The patient was also given zoledronic acid during his hospital course and was discharged to a subacute rehab center. Neurosurgery was consulted during the hospital stay and recommended conservative management for his T11 and T12 fractures. Patient was instructed to stop abiraterone acetate indefinitely, as it should have been stopped in 2022 after 2 years in combination with ADT as per the STAMPEDE trial [1].

3. Discussion

Adrenal insufficiency induced by abiraterone acetate is a rare but serious adverse event that arises due to the drug's inhibition of CYP17A1, which leads to a reduction in cortisol production. This can result in primary adrenal insufficiency. That is why it is always given with prednisone/prednisolone [1,2,4,5]. The most likely pathophysiology involves the suppression of adrenal gland function due to a lack of necessary precursors for cortisol synthesis, resulting in impaired steroidogenesis and inability to mount an adequate glucocorticoid response, especially in times of stress.

CYP17 inhibition can result in high ACTH because of inhibited steroidogenesis which can lead to the formation of excess precursors upstream of CYP17 resulting in mineralocorticoid excess syndrome (MES). This pathogenesis is similar to that of the 17 alpha hydroxylase's deficiency which is a CYP17A1 in congenital adrenal hyperplasia (CAH) in which upstream substrate, corticosterone accumulates and acts also as a weak glucocorticoid and sometimes, at very high levels, suppresses ACTH [6]. This mineralocorticoid excess, together with the weak glucocorticoid activity usually mitigate the clinical consequences of adrenal insufficiency [7]. This parallel between abiraterone acetate and CAH led the investigators awareness away from the potential of abiraterone acetate to induce adrenal insufficiency in the early trials that utilized abiraterone acetate in the treatment of prostate cancer. In the initial phase I and II trials, abiraterone acetate was administered with and without glucocorticoid therapy in castrate and non-castrate prostate cancer patients. In one trial that monitored cortisol level and performed cosyntropin testing in patients receiving abiraterone acetate, it was found that although there was no overt adrenal insufficiency, there was observed reduction in cortisol levels and suboptimal response to cosyntropin stimulation test in a few patients [8]. In another phase I trial that evaluated abiraterone acetate in patients with castrate-resistant prostate cancer who were previously on ketoconazole, MES occurred which was treated with aldosterone receptor antagonist [9]; however, the adjunct glucocorticoid therapy also had the additional effect of improving tumor response as well as ameliorated the incidence of MES occurrence [10,11]. These findings established the role of glucocorticoids coadministration in phase III trials. Prednisone 10 mg once a day was given concurrently with abiraterone in COU-AA-301/302, while prednisone 5 mg was given in the STAMPEDE and LATITUDE trials [1,2,4,5]. Despite the drastic decreased incidence of MES occurrence, fatigue, which was queried to be implicative of AI, was the commonest side effect.

Symptoms of adrenal insufficiency can be nonspecific and may include fatigue, hypotension, dizziness, weight loss, and electrolyte disturbances such as hyperkalemia and hyponatremia. As seen in our very atypical case of a patient of localized prostate cancer, 5 years in remission with the anticipation of them being off treatment, meticulous medications review, and early identification of symptoms is important. Fatigue, hypotension and dysphagia leading up to FTT were the side effects seen in our patient.

 doi:10.20944/preprints202502.1404.v1

Treatment in patients receiving active treatment include increasing corticosteroid dose. In our patient with high risk localized prostate cancer with 5 years in remission and T PSA <0.1 checked during hospitalization, we discontinued abiraterone acetate and initiated corticosteroid replacement therapy with hydrocortisone, which improved his symptoms drastically. Close monitoring of electrolytes, blood pressure, and cortisol levels is essential in managing these patients.

4. Conclusion

This case highlights the potential for abiraterone acetate to induce adrenal insufficiency, a serious but treatable side effect, especially at times of stress and when given in a wrong manner without concurrent corticosteroids. Adrenal insufficiency can still also occur in patients receiving abiraterone with concurrent corticosteroids. Currently, there is no evidence to support whether the 5 mg or the 10 mg dose of prednisone is superior in patients receiving active treatment with abiraterone. When choosing, one must weigh the risk of abiraterone possible side effects of AI as opposed to adverse events related to hypercortisolism. However, there is evidence to support both. Non oncology Clinicians also should be cognizant of this risk, particularly in patients presenting with unexplained nonspecific symptoms particularly fatigue, hypotension and failure to thrive and with no clear indication to be on such medication. They should undergo decent review of patients' medications. Early diagnosis and prompt treatment with corticosteroid replacement therapy are crucial. Further research is still needed to better understand the mechanisms and incidence of adrenal insufficiency in patients treated with abiraterone acetate.

References

1. Fizazi, K.; Tran, N.; Fein, L.; Matsubara, N.; Rodriguez-Antolin, A.; Alekseev, B.Y.; Özgüroğlu, M.; Ye, D.; Feyerabend, S.; Protheroe, A.; et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N. Engl. J. Med.* **2017**, *377*, 352–360, https://doi.org/10.1056/nejmoa1704174.
2. Chi, K.N.; Protheroe, A.; Rodríguez-Antolín, A.; Facchini, G.; Suttman, H.; Matsubara, N.; Ye, Z.; Keam, B.; Damião, R.; Li, T.; et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. *Lancet Oncol.* **2018**, *19*, 194–206, https://doi.org/10.1016/s1470-2045(17)30911-7.
3. Reid, A.H.; Attard, G.; Barrie, E.; de Bono, J.S. CYP17 inhibition as a hormonal strategy for prostate cancer. *Nat. Rev. Endocrinol.* **2008**, *5*, 610–620, https://doi.org/10.1038/ncpuro1237.
4. De Bono, J.S.; Logothetis, C.J.; Molina, A.; Fizazi, K.; North, S.; Chu, L.; Chi, K.N.; Jones, R.J.; Goodman, O.B.,Jr.; Saad, F.; et al. Abiraterone and Increased Survival in Metastatic Prostate Cancer. *N. Engl. J. Med.* **2011**, *364*, 1995–2005, https://doi.org/10.1056/nejmoa1014618.
5. Ryan, C.J.; Smith, M.R.; De Bono, J.S.; Molina, A.; Logothetis, C.J.; De Souza, P.; Fizazi, K.; Mainwaring, P.; Piulats, J.M.; Ng, S.; et al. Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. *N. Engl. J. Med.* **2013**, *368*, 138–148. https://doi.org/10.1056/nejmoa1209096.
6. Auchus, R.J. THE GENETICS, PATHOPHYSIOLOGX, AND MANAGEMENT OF HUMAN DEFICIENCIES OF P450c17. *Endocrinol. Metab. Clin. North Am.* **2001**, *30*, 101–119, https://doi.org/10.1016/s0889-8529(08)70021-5.
7. Moreira, A.C.; Leal, A.M.O.; Castro, M. Characterization of Adrenocorticotropin Secretion in a Patient with 17α-Hydroxylase Deficiency*. *J. Clin. Endocrinol. Metab.* **1990**, *71*, 86–91, https://doi.org/10.1210/jcem-71-1-86.
8. O'Donnell A, Judson I, Dowsett M, Raynaud F, Dearnaley D, Mason M, et al. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer. 2004 Jun 14;90(12):2317–25.
9. Ryan, C.J.; Smith, M.R.; Fong, L.; Rosenberg, J.E.; Kantoff, P.; Raynaud, F.; Martins, V.; Lee, G.; Kheoh, T.; Kim, J.; et al. Phase I Clinical Trial of the CYP17 Inhibitor Abiraterone Acetate Demonstrating Clinical

 doi:10.20944/preprints202502.1404.v1

Activity in Patients With Castration-Resistant Prostate Cancer Who Received Prior Ketoconazole Therapy. *J. Clin. Oncol.* **2010**, *28*, 1481–1488, https://doi.org/10.1200/jco.2009.24.1281.

10. Attard, G.; Reid, A.H.; A'Hern, R.; Parker, C.; Oommen, N.B.; Folkerd, E.; Messiou, C.; Molife, L.R.; Maier, G.; Thompson, E.; et al. Selective Inhibition of CYP17 With Abiraterone Acetate Is Highly Active in the Treatment of Castration-Resistant Prostate Cancer. *J. Clin. Oncol.* **2009**, *27*, 3742–3748, https://doi.org/10.1200/jco.2008.20.0642.
11. Decamps, S.; Lis, R.; Ekanayake, P. Abiraterone-Induced Endocrinopathies. *Jcem Case Rep.* **2023**, *1*, luad039, https://doi.org/10.1210/jcemcr/luad039.