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Cardiac Arrhythmia and Heart Failure Related to Abiraterone Use: A Case Report.

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KEYWORDS

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ABSTRACT:

Cancer therapy has improved survival, and, because the population aging, cancer and cardiovascular disease have a high and superposed incidence. In addition, some therapies can lead to myocardial damage and other cardiovascular consequences. Of the chemotherapy drugs, the action of anthracyclines on the heart has been the most extensively studied since the 1960s. More recently, therapies targeting the HERS-2 receptor were also associated with cardiotoxicity. Other therapies, such as hormonal blockades, have also been related to cardiac manifestations, among them abiraterone, which has been associated, in case series, with metabolic changes, hypertension, arrhythmias, and heart failure. We report the case of an 80-year-old man undergoing treatment for advanced prostate cancer who sought cardiac care, complaining of nocturnal tachycardia. He had a history of two previous surgeries, prostatectomy, and orchiectomy, 15 years ago. Various therapies for advanced prostate cancer were tried. For the past two years, he had been using abiraterone and goserelin. He also had hypertension and dyslipidemia and used metoprolol, chlorthalidone, and rosuvastatin. He was hypertensive and bradycardic on physical examination, with extra-systoles on auscultation. Electrocardiogram with sinus bradycardia, conduction disturbance in the right branch, and U wave, with one supraventricular extra-systole. Laboratory examination showed hypokalemia (2.9 mg/dl). Holter 24h showed sustained atrial tachycardia for most of the night. The echocardiogram showed a decrease in the ejection fraction and an increase in the left atrium and ventricle measures compared to another performed two years ago. Since the suspension of the hormone blocker was not feasible, treatment included diuretic exchange for spironolactone, potassium supplementation, ramipril, and metoprolol. There was a symptomatic recovery in 30 days and ventricular function in 6 months. He lived for two years and died after a home fall and trauma complications. The possible explanation of abiraterone cardiovascular effects is the action on the adrenal, with an inhibitory synthesis of sexual hormones and cortisol; this should be responsible for heart function decrease, arrhythmias, and hypokalemia due to the high mineralocorticoid overproduction in the absence of negative feedback by cortisol. However, clinicians need to be aware of these risks.

1. INTRODUCTION

The evolution of cancer treatment preserved millions of lives and contributed to the population aging. Nowadays, clinicians need to work with cancer survivors, which present cancer sequelae and the possibility of cancer treatment side effects. Cardiology societies' concerns, expressed in the guidelines for cardio-oncology assessments and medical treatment, have increased in the last decade.[1]

Since the 1960s, the cardiovascular actions of anthracyclines have been a study object. Therefore, there have been many descriptions of cardiotoxicity of cancer drugs in the past decades. Other therapies, such as the HERS-2 receptor targeting, were also associated with cardiotoxicity.[2] Hormonal blockade therapies had a historical landmark in 1941. However, the most extensive research was conducted in the 1980s, when total hormonal blockade, using androgenic blockade in

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association with a luteinizing hormone-releasing hormone (LHRH) agonist, was proposed to block androgens of both testicular and adrenal synthesis. The safe-effectivity studies showed that the most frequent side effects were gynecomastia and flashes, with low rates of cardiovascular consequences.[3-5] In the last decade, some case reports or series presented cardiovascular side effects of this therapy. [6-10.]

2. OBJECTIVE

Since people are surviving long years after a cancer diagnosis and treatment, cardiologists are interested in the consequences of cancer treatment. The objective is to describe a clinical case of an 80-year-old man in advanced prostate cancer treatment with hormonal blockage, which evolved with cardiac features.

3. CASE REPORT

An 80-year-old man undergoing treatment for advanced prostate cancer came to the cardiologist's office complaining of palpitations. He had a history of two previous surgeries, prostatectomy, and orchiectomy, for 15 years and used various therapies for advanced prostate cancer. In the past two years, he received Abiraterone and Goserelin. He was on arterial hypertension and dyslipidemia treatment, with Metoprolol 100 mg/day, Chlorthalidone 25 mg/day, and Rosuvastatin 10 mg/day. Physical examination showed blood pressure (BP) of 176/100 mmHg, heart rate (HR) of 48 bpm, extra-systoles on auscultation, without murmurs, and no other findings. ECG (Figure 1) had sinus bradycardia, conduction disturbance in the right branch, and U wave, with one supraventricular extra-systole.

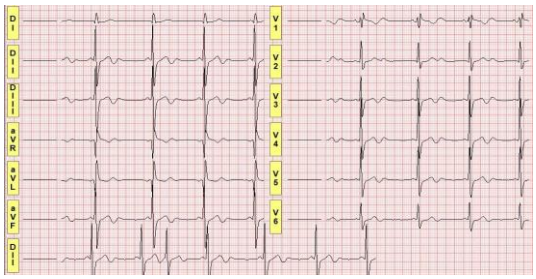

Figure 1. Initial ECG. Source: the authors.

Biochemistry showed lipids controlled, fasting glucose= 109 mg/dL, glycated hemoglobin= 6.2%, creatinine 1.27 mg/dL sodium= 145 mEq/L, potassium= 2.9 mEq/L, and TSH= 1,592 mU/L. A 24h-holter, done four months ago, demonstrated sustained atrial tachycardia during almost the entire night, and an echocardiogram performed two years ago, with normal systolic function. The initial management was stopping chlorthalidone and starting spironolactone and enalapril while metoprolol was maintained. Two weeks after he was asymptomatic, potassium levels were normal (4.2 mEq/L), BP= 140/90 mmHg, and HR= 60 bpm, without significant findings on physical examination. A new echocardiogram showed decreased systolic function, and a new 24h-holter reported rare atrial tachycardias, always lasting less than 5 seconds (Figures 2 and 3. Table 1).

The patient's onco-urologist opinion was that there were poor alternatives to the in-course treatment, which was maintained.

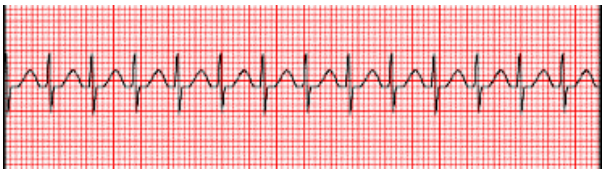

Figure 2. Atrial tachycardia in the first 24h-holter. Source: the authors.

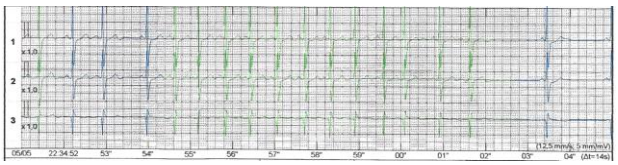

Figure 3. Short run of atrial tachycardia after medical management. Source: the authors

Table 1. Sequential echocardiograms.

	2019	2020	2021
Left atrium (mm)	40	44	42
Aorta (mm)	38	39	39
Right ventricle (mm)	12	12	12
Septum (mm)	12	14	14
Posterior wall (mm)	16	16	15
Left ventricle diastolic diameter (mm)	48	44	44
Left ventricle systolic diameter (mm)	22	34	31
Left ventricle shortening (%)	46	23	30
Left ventricle ejection	72	48	63

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fraction (%)			

Source: the authors

The patient remained asymptomatic for the next two years. Unfortunately, at this time, he had at home, with significant trauma complications, and died after a three-day hospitalization. The in-hospital assessment after the fall showed no metabolic or cardiac disorders.

4. DISCUSSION

Abiraterone acetate is a hormone blocker of androgens and corticosteroid synthesis at the level of the adrenal gland by acting on the enzyme CYP-17, decreasing the synthesis of sex hormones and cortisol.[4] Effectivity trials have shown low rates of cardiovascular side effects.[2,5] The use of these substances was associated, however, in pharmacovigilance studies, with reduced ventricular function and arrhythmias.6 The risk of a patient on Abiraterone treatment to get into hospital with atrial fibrillation is 12% higher than those using enzalutamide, another hormone blocker.9 There are case reports and series describing cardiovascular damage, and a recent meta-analysis suggested an association of Abiraterone with cardiotoxicity.10

As the present case showed, Bretagne et al.[6] and Scailteux et al.[11] also reported the specific finding of atrial arrhythmia.

Uncontrolled hypertension associated with hypokalemia, as seen in this case, is rare in some series4 and frequent in others.[9] The proposed mechanism for hypertension and hypokalemia is the overproduction of mineralocorticoids, given the absence of negative feedback by cortisol, leading to potassium renal loss.[8] Thiazide diuretics should be avoided concomitantly with Abiraterone due to the possibility of severe hypokalemia[6], just like the present case. The substitution of chlorthalidone for spironolactone successfully restored potassium levels and helped hypertension control. Thus, the patient had a symptomatic gain two weeks after therapeutical adjustment. In this case, myocardial dysfunction, atrial arrhythmia, hypertension, and hypokalemia with electrocardiographic manifestations were detected.

Goserelin acetate, an LHRH agonist used in this patient, has a less deleterious action on the cardiovascular system compared to adrenal androgen blockers; the isolated use of Goserelin had 1.1% cardiovascular effects compared to 2.2% in patients who used Cyproterone alone; the combination therapy was equally safe in this study. The same authors observed that critical cardiovascular effects motivating therapy discontinuation occurred in half of the cases.[5]

A recent review observed metabolic effects in overweight, reduced insulin sensitivity, and dyslipidemia with anti-androgenic therapy.[11] The patient reported having dyslipidemia, without overweight or glucose disturbances.

Cardiovascular mortality was not affected by using LHRH agonists in a retrospective analysis in an 8-year follow-up.[12] This information was supported by a meta-analysis investigating short-term and long-term cardiovascular risk of death.[13]

However, in men with known cardiovascular disease, the use of a LHRH agonist was associated with 30% higher risk of cardiovascular events compared with untreated patients. Although there is conflicting evidence, the medical associations suggest a possible association between androgen antagonist therapy and the risk of CV events, with statements to inform the cardiovascular risk, diabetes risk, and the need to work in cardiovascular risk factors in users of LHRH agonists.[14]

Men with advanced prostate cancer are usually older adults, requesting strict monitoring and assessment for frailty and polypharmacy.[12] The cardiovascular risk, however, rises with age, and cardiotoxic drugs with metabolic changes in a heart with atrial arrhythmia susceptibility can be very dangerous.[15,16.]

Patients with cancer and cardiac risk or diseases will be routine, so cardiologists must know the risks of cancer therapy. Patients undergoing chemotherapy need supervision and regular ventricular function and arrhythmia assessment.[1,2.]

Patients using hormone blockers, such as Abiraterone, should be carefully assessed for the risk of cardiotoxicity.[10]

Clinicians should avoid hypokalemia-inducing drugs, such as thiazides or beta-2-agonists, in association with adrenal androgen blocker agents.6 Cardiac arrhythmia is an important finding, and atrial tachycardia or atrial fibrillation can occur in these patients.[6,10.]

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Sometimes, the hormone blockade therapy cannot be interrupted, and then cardiologists, urologists, and oncologists need to be in contact for the patient's benefit.[1]

5. CONCLUSION

Abiraterone may induce myocardial dysfunction, tachyarrhythmias, hypokalemia, and hypertension, as described in this case. Clinicians must carefully monitor patients undergoing hormone blockade therapy for advanced prostate cancer.

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