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CASE REPORT

Cancer therapeutics-related cardiac dysfunction in a patient treated with abiraterone for castration-resistant prostate cancer

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Abstract

Abiraterone is an agent effective for castration-resistant prostate cancer, but there have been no reports of cardiotoxic effects inducing cardiomyopathy, to our knowledge. We present a case of an 86-year-old man with castration-resistant prostate cancer treated with abiraterone. He had received an androgen receptor antagonist (bicalutamide) and a gonadotropin-releasing hormone antagonist (degarelix) for 3 years. These agents were changed to enzalutamide due to elevation of plasma prostate-specific antigen level of 129 ng/mL. One year later, the oral androgen receptor inhibitor (enzalutamide) caused drug-induced lung injury and was changed to abiraterone. Transthoracic echocardiography (TTE) revealed normal left ventricular systolic function, and left ventricular ejection fraction (LVEF) was 67%. Four weeks after administration of abiraterone, he complained of dyspnea on effort and bilateral leg edema, and he was diagnosed with heart failure. TTE showed hypokinesis of the diffuse LV, and LVEF decreased to 45%. The various causes of heart failure were excluded. Since a cardiotoxic effect of abiraterone was suspected, administration of abiraterone was discontinued. Two weeks after cessation of abiraterone, LVEF ameliorated to 57%, and then 5 months after cessation of abiraterone, LVEF further improved to 65%. To our knowledge, this is the first report of definite cancer therapeutics-related cardiac dysfunction due to a hormonal agent such as abiraterone diagnosed according to the American Society of Echocardiography and European Association of Cardiovascular Imaging criteria.

Keywords Echocardiography · Cardiac toxicity · Chemotherapy · Cardio-oncology · Hormonal therapy

Introduction

Abiraterone is a novel agent for castration-resistant prostate cancer, which can inhibit the extra-gonadic production of testosterone by inhibiting the enzyme activity of steroid 17alpha-monooxygenase. Recently, abiraterone has been reported to show cardiotoxicity such as myocardial infarction, supraventricular tachycardia, and ventricular tachycardia [1, 2]. But there have been no reports of cardiomyopathy due to abiraterone. Cancer therapeutics-related cardiac dysfunction (CTRCD) is a collective term for cardiac disorders induced by drug treatment. CTRCD is defined as a decrease in the left ventricular ejection fraction (LVEF) of greater than 10 percentage points, to a value < 53% after administration of the therapeutic agent, and is classified into reversible type and irreversible type [3, 4]. Here, we report a case of the reversible type of CTRCD possibly induced by abiraterone.

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Case report

An 86-year-old man was diagnosed with prostate cancer and had received an androgen receptor antagonist (bicalutamide) and a gonadotropin-releasing hormone antagonist (degarelix) for 3 years. These agents were changed to an androgen receptor inhibitor (enzalutamide) due to elevated plasma prostate-specific antigen (PSA) level of 129 ng/mL. One year later, enzalutamide caused drug-induced lung injury, after which enzalutamide was changed to abiraterone. Two weeks before administration of abiraterone, transthoracic echocardiography (TTE) showed almost normal findings including LV size and systolic function, and no evidence of valvular disease or congenital heart disease. LV volume and LVEF were assessed by modified biplane Simpson's method (Table 1; Figs. 1a, 2a). Four weeks after administration of abiraterone, he complained of dyspnea on effort and bilateral leg edema. Auscultation revealed the third heart sound and no cardiac murmur. Chest X-ray showed bilateral pleural effusion and pulmonary congestion. Plasma brain natriuretic peptide level was 239 pg/mL, and PSA was 505 ng/mL (Table 1). He was diagnosed with heart failure and admitted to our hospital. Laboratory examination revealed no evidence of elevated cardiac enzymes, thyroid disease, or viral infection. Electrocardiography showed no findings indicating ischemic heart disease, myocarditis, or arrhythmias. Coronary angiography revealed no significant stenoses in coronary arteries. TTE revealed hypokinesis of the diffuse LV and that LVEF decreased to 45% (declined by 12% from baseline), and no evidence of significant valvular disease (Table 1; Figs. 1b, 2b). Collectively, these findings suggested that the cause of heart failure was LV systolic dysfunction possibly induced by abiraterone, and abiraterone was withdrawn. Two weeks after cessation of abiraterone, PSA deteriorated to 515 ng/mL, but LVEF ameliorated to 57% (Table 1; Figs. 1c, 2c). This condition met the diagnostic criteria of definite CTRCD defined by the American Society of Echocardiography and European Association of Cardiovascular Imaging [3] as LVEF more than 53% before cancer therapeutics and decrease by greater than 10% after hormonal therapy. And then 5 months after cessation of abiraterone, PSA elevated to an extremely high level of 7806 ng/mL, but LVEF further improved to 65% (Table 1; Figs. 1d, 2d).

Discussion

Prostate cancer is the most commonly found cancer in men. Androgen deprivation therapy is the standard treatment for advanced prostate cancer [5]. Although most patients initially respond to castration with luteinizing hormone-releasing analogs or bilateral orchiectomy, tumors can subsequently progress to castration-resistant prostate cancer [6]. Abiraterone is able to inhibit the extra-gonadic production of testosterone by inhibiting the enzyme activity of steroid 17alpha-monooxygenase, which is a member of the cytochrome p450 family that catalyzes the 17alpha-hydroxylation of the steroid intermediates involved in testosterone synthesis, or the direct inhibition of androgen receptor activity [7]. Although the incidence of cardiac events such as myocardial infarction, supraventricular tachycardia, and ventricular tachycardia has been reported in approximately 15% of castration-resistant prostate cancer patients who received abiraterone, there are no reports of

Table 1 Time course of echocardiographic data of the presented case before and after abiraterone administration

	2 weeks before administration	4 weeks after administration	2 weeks after cessation	5 months after cessation
LVEDVi (mL/m^2)	55	43	57	47
LVESVi (mL/m^2)	18	23	24	13
LVSVi (mL/m^2)	37	19	33	35
LVEF (%)	67	45	57	65
LAD (mm)	27	39	36	32
LAV (mL)	37	50	47	37
LAVi (mL/m^2)	23	31	29	23
E (cm/s)	52	69	68	82
A (cm/s)	50	26	43	67
E/*A* ratio	1.0	2.6	1.6	1.2
E' (cm/s)	5.0	4.0	6.5	8.0
E/*E*' ratio	11	16	11	10

PSA prostate-specific antigen, *LVEDVi* left ventricular end-diastolic volume index, *LVESVi* left ventricular end-systolic volume index, *LVSVi* left ventricular stroke volume index, *LVEF* left ventricular ejection fraction; *LAD,* left atrial diameter; LAV, left atrial volume; LAVi, left atrial volume index

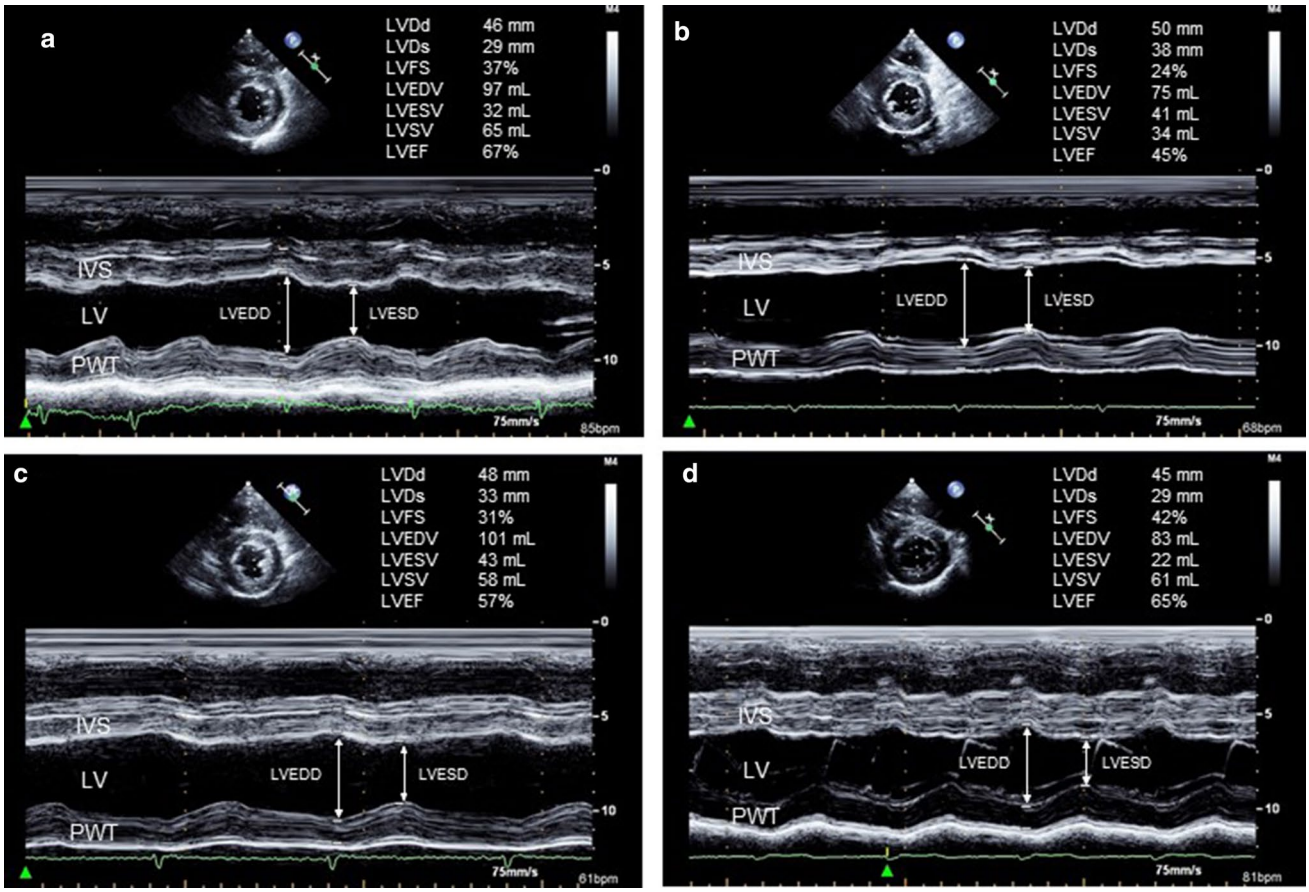

Fig. 1 M-mode echocardiography of the presented case. **a** 2 weeks before administration, **b** 4 weeks after administration, **c** 2 weeks after cessation, and **d** 5 months after cessation of abiraterone. LVEF was decreased at 4 weeks after administration of abiraterone (**b**), which improved 2 weeks after cessation of abiraterone (**c**). Further improvement of LVEF was noted 5 months after cessation of abiraterone (**d**). *LV* left ventricle, *IVS* interventricular septum, *PWT* inferolateral wall thickness, *LVDd* LV end-diastolic dimension, *LVDs* LV end-systolic dimension, *LVFS* LV fractional shortening, *LVEDV* LV end-diastolic volume, *LVESV* LV end-systolic volume, *LVFS* LV stroke volume, *LVEF* LV ejection fraction

cardiomyopathy induced by abiraterone [1, 2]. CYP17 is the key enzyme inhibited by abiraterone, which bears components of 17alpha-hydroxylase and 17, 20-lyase and mediates androgen and cortisol synthesis. As a result of inhibiting CYP17, the level of aldosterone is elevated, and the levels of cortisol and dihydrotestosterone are suppressed (Fig. 3). We considered the possibility of increased concentration of mineral corticoid by inhibiting CYP17, and resultant water retention and hypertension for the development of heart failure. However, in our case, the serum concentration of sodium or potassium or blood pressure did not change after administration of abiraterone. The precise mechanism of cardiac toxicity is unknown. CTRCD is a collective term for myocardial disorders induced by drug treatment. CTRCD is defined as a decrease in the LVEF of greater than 10 percentage points, to a value < 53% after chemotherapy. CTRCD is classified into two types; type 1 CTRCD is dose-dependent and irreversible, and type 2 CTRCD is not dose-related and reversible [3]. In our case, LVEF decreased from 67 to 48% at 6 weeks after administration of abiraterone, and it recovered to 73% at 5 months after discontinuation of abiraterone. Therefore, we diagnosed type 2 CTRCD. Type 2 CTRCD has thus far only been reported in patients who received molecularly targeted drugs such as trastuzumab, lapatinib, pertuzumab, imatinib, sorafenib, sunitinib, bevacizumab, and bortezomib [3]. To our knowledge, this is the first report of definite CTRCD caused by a hormonal agent such as abiraterone, but further investigation is warranted to further address various issues such as its incidence rate, the timing of onset, and risk factors.

Conclusions

We presented a case of type 2 CTRCD due to the new hormonal agent abiraterone. To our knowledge, this is the first report of definite CTRCD caused by a hormonal

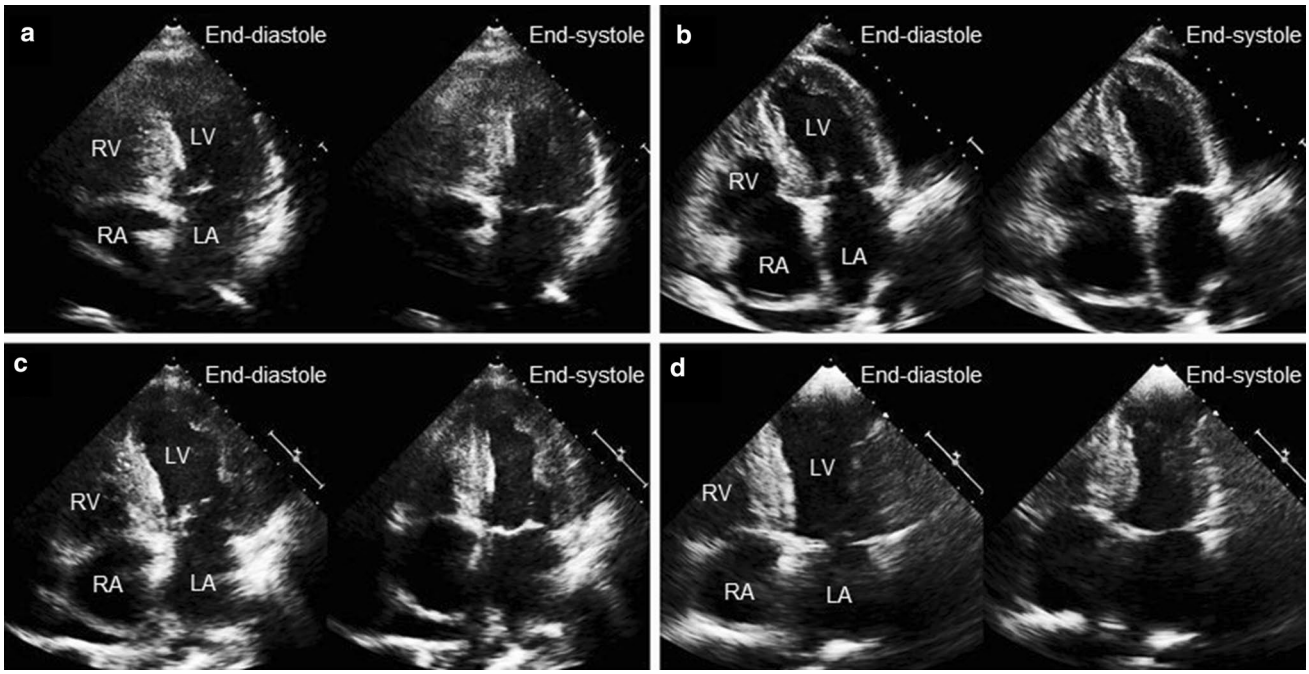

Fig. 2 Transthoracic echocardiograms of the apical four-chamber view. **a** 2 weeks before administration, **b** 4 weeks after administration, **c** 2 weeks after cessation, and **d** 5 months after cessation of abiraterone. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle

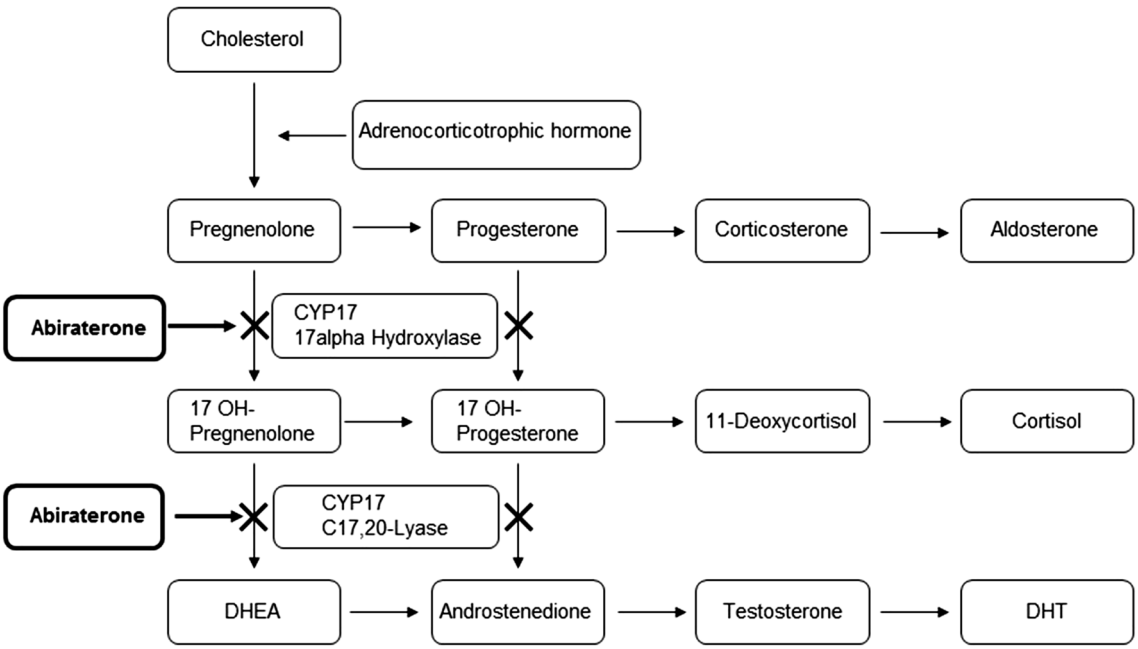

Fig. 3 Steroid synthesis pathways. Abiraterone inhibited CYP17, resulting in the elevation of aldosterone and the suppression of cortisol and dihydrotestosterone. *DHEA* dihydroepiandrostenedione, *DHT* dihydrotestosterone

agent such as abiraterone. These findings highlight the need for caution in following patients who receive abiraterone, and further might suggest the clinical significance of periodic evaluation of cardiac function for those who

receive hormonal agents including abiraterone to treat prostate cancer.

Compliance with ethical standards

Human rights statement and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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