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Case report

Frequent premature ventricular contractions induced by fluconazole: A case report

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ABSTRACT

Introduction: Fluconazole is commonly used to treat and prevent fungal infections caused by Candida and Cryptococcus species. Although there have been reports of fatal arrhythmias induced by fluconazole, such as torsades de pointes, there have been minimal reports of mild, non-fatal arrhythmias associated with it, which may have been overlooked in clinical practice. We encountered a case of frequent premature ventricular contractions induced by fluconazole during the treatment of HIV-related pulmonary cryptococcosis. Herein, we report a case of frequent premature ventricular contractions (PVCs) induced by fluconazole, along with a literature review.

Case presentation: A 47-year-old man diagnosed with human immunodeficiency virus-related pulmonary cryptococcosis experienced an irregular heartbeat during antifungal therapy with fluconazole at 400 mg once daily. A 12-lead electrocardiogram was conducted, which displayed frequent unifocal PVCs originating in the right ventricular outflow tract without QT prolongation. After reducing the dose of fluconazole to 200 mg once daily, the patient's symptoms slightly improved, and PVC frequency decreased on a 12-lead ECG; however, PVCs did not disappear. After discontinuing fluconazole, the symptoms improved, and a follow-up 12-lead electrocardiogram showed no PVCs.

Conclusions: We encountered the case of frequent PVCs induced by fluconazole during the treatment of human immunodeficiency virus-related pulmonary cryptococcosis. Furthermore, it was suggested that the PVC frequency was dose-dependent for fluconazole. Careful follow-up for new-onset arrhythmias and ECG evaluations are essential before and after fluconazole administration.

Introduction

Some antimicrobials adversely affect cardiac activity [1–3]. Fluconazole (FLZ) is one of the azoles widely used in the treatment and prevention of fungal infections caused by Candida and Cryptococcus species. Although FLZ is a well-tolerated drug, it is known to have cardiac side effects such as QT prolongation and fatal torsades de pointes (TdP) [4–6]. Although there have been reports of fatal arrhythmias induced by FLZ, there have been very limited reports of mild, non-fatal arrhythmias associated with it. We encountered a case of frequent premature ventricular contractions (PVCs) induced by FLZ during the treatment of human immunodeficiency virus (HIV)-related pulmonary cryptococcosis. Furthermore, in this case, we could observe that PVCs were induced by FLZ dose-dependently. Herein, we report PVCs induced by FLZ, which may have been overlooked previously, along with a literature review.

Case report

A 47-year-old man with hypertension was admitted to another hospital with a history of dry cough, dyspnea, and low-grade fever persistent for a month. He was diagnosed with *Pneumocystis jirovecii* pneumonia (PCP) and acquired immune deficiency syndrome, with a CD4 count of 94 cells/μL and HIV-RNA of 2,500,000 copies/mL. After treatment with a 21-day course of antibiotics and prednisone for PCP, chest computed tomography (CT) was conducted which revealed

Abbreviations: Cr-Ag, cryptococcal antigen; CT, computed tomography; ECG, electrocardiogram; FLZ, fluconazole; HIV, human immunodeficiency virus; PCP, *Pneumocystis jirovecii* pneumonia; PVC, premature ventricular contraction; TdP, torsades de pointes.

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multiple newly developed nodules in the right upper lobe of the lung. For further examination and treatment, the patient was transferred to our hospital.

Upon thorough examination, the patient was found to have developed oral candidiasis; hence, he was started on a treatment with oral FLZ 200 mg once daily (defined as day 0). The following day, antiretroviral therapy with bictegravir, emtricitabine, and tenofovir alafenamide was initiated for treating HIV infection (day 1). Meanwhile, his serum cryptococcal antigen (Cr-Ag) level, measured after transfer to our hospital, was found to be 1:128, and it was suspected that the previously detected pulmonary nodule was pulmonary cryptococcosis. As the neurological and head magnetic resonance imaging findings were normal, we considered that the patient had not developed cryptococcal meningitis. On day 9, bronchoscopy was performed to examine the lung nodules, and the FLZ dose was increased to 400 mg once daily from the following day (day 10). Although no microbiological findings indicating the presence of cryptococcosis were obtained from the bronchoscopy samples, we decided to continue FLZ at 400 mg once daily because his clinical course strongly suggested pulmonary cryptococcosis. Shortly after increasing the FLZ dose, the patient became aware of occasional heartbeat-skipping symptoms, which persisted thereafter. The patient was discharged from our hospital on day12 with no other symptoms. Subsequently, the patient was in a good condition, but the symptoms of a skipping heartbeat persisted to the same degree (Fig. 1). On day 83, frequent unifocal PVCs originating in the right ventricular outflow tract without QT prolongation were detected on a 12-lead electrocardiogram (ECG) (Fig. 2) (Fig. 3b). These PVCs had not been observed on a 12-lead ECG conducted upon the patient's admission to our hospital (day −5) (Fig. 3a).

We suspected that the arrhythmia was induced by FLZ, as symptomatic PVCs only occurred after the FLZ dose was increased. However, we decided to continue its use for the following reasons: PVCs originating from the right ventricular outflow tract are commonly considered benign, and FLZ is a first-line antifungal agent for mild pulmonary cryptococcosis. From day 84, FLZ was continued at a reduced dose of 200 mg once daily with careful monitoring of the patient's symptoms. After dose reduction, the frequency with which the patient felt a skipping heartbeat decreased. Additionally, a decrease in the frequency of PVCs was observed on day 111 (Fig. 3c). On day 170, the patient's chest CT scan showed that the lung nodules had almost disappeared, and the serum Cr-Ag level had also decreased; however, PVCs persisted on a 12-lead ECG (Fig. 3d). On day 175, FLZ treatment was discontinued because the arrhythmias had persisted despite the dose reduction. On day 202, the patient had no apparent complaints or abnormal findings on a 12-lead ECG (Fig. 3e). The clinical course, main findings, and all concomitant medications used for the patient are shown in Fig. 1. No electrolyte abnormalities requiring therapeutic intervention were observed during the clinical course shown in Fig. 1. The patient had been taking hypertension medications before admission to the previous hospital, but the hypertension treatment had been discontinued during the admission. As his blood pressure gradually increased after the transfer to our hospital, amlodipine and irbesartan were started at days 27 and 34, respectively. After the initiation of the hypertension treatment, the patient's blood pressure remained at approximately 130/80 mmHg.

Discussions

Although azoles are known to cause QT prolongation leading to TdP [4–6], there are very limited reports of non-fatal arrhythmias associated with these drugs. While there is a report of drug-induced PVCs due to itraconazole [7], to our knowledge, there have been no similar reports on FLZ. We encountered a case of frequent PVCs induced by FLZ during the treatment of HIV-related pulmonary cryptococcosis. Furthermore, the PVCs that occurred after increasing the dose of FLZ to 400 mg daily improved after discontinuation of the antifungal treatment.

PVCs are commonly associated with structural heart diseases and systemic health conditions such as hypertension, hypoxia, and electrolyte abnormalities [8]. In addition, a high HIV viral load and low CD4 count have been reported to potentially increase the risk of ventricular arrhythmias [9,10]. In this case, these factors should be considered for the PVC development. At the time of transfer to our hospital, the patient had untreated hypertension and HIV infection without any history of heart disease. There were no symptoms or abnormal ECG findings at the time of admission to our hospital (day −5) and symptomatic PVCs developed later. Therefore, it is reasonable to consider that the occurrence of PVCs was mainly associated with a change in condition or additional interventions after admission to our hospital. Considering that PVCs improved after FLZ discontinuation, it is plausible that PVCs were primarily induced by it.

The patient received several concomitant medications for HIV infection and hypertension during FLZ use for cryptococcosis. FLZ is a moderate inhibitor of CYP3A4, and the clinical interactions of CYP3A substrates with FLZ should be considered when used at doses of more than 200 mg daily [11]. Serum concentrations of bictegravir and amlodipine, which are CYP3A substrates, may increase after co-administration with FLZ. The serum concentration of irbesartan, a substrate and mild inhibitor of CYP3A, has been reported to increase slightly after FLZ co-administration [12]. Among the drugs that could have been affected by the concomitant use of FLZ, amlodipine and irbesartan were started after the onset of symptoms and were unlikely to

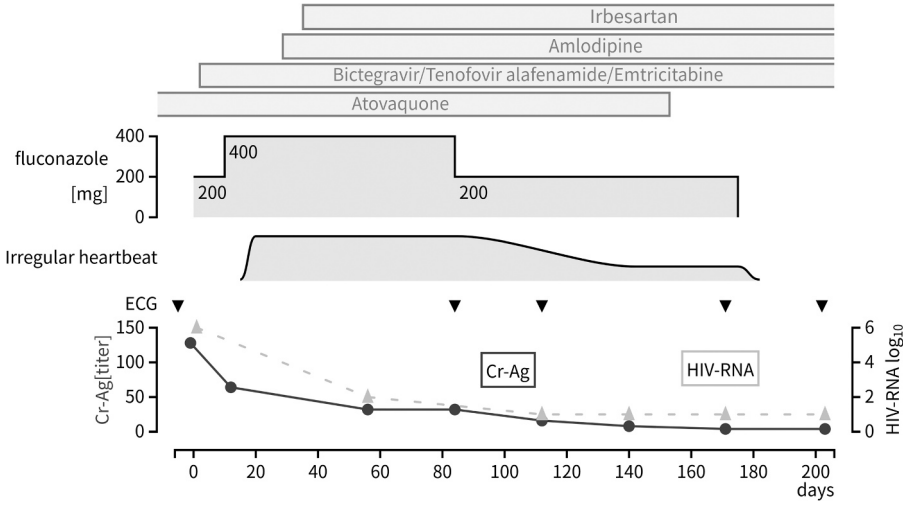

Fig. 1. The clinical course. Abbreviations: Cr-Ag, cryptococcal antigen; HIV, human immunodeficiency virus; ECG, electrocardiogram.

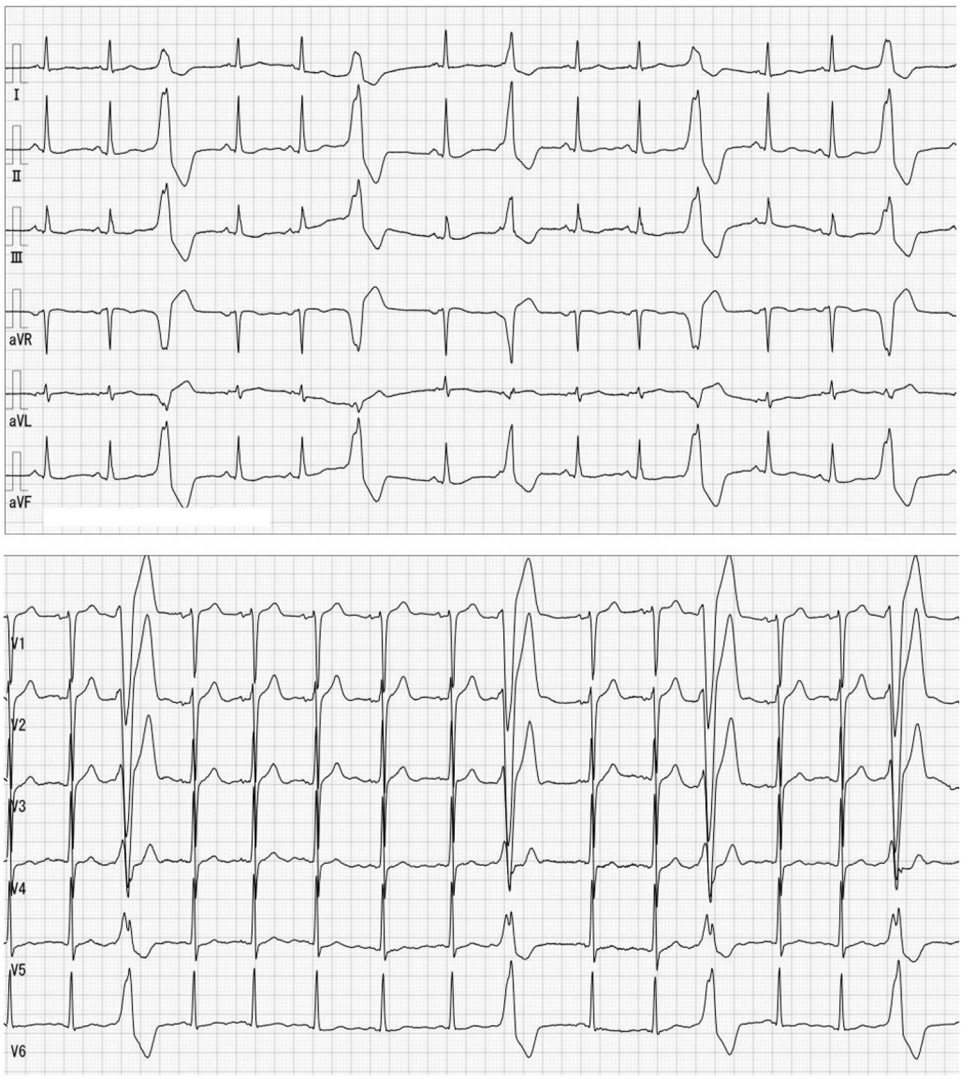

Fig. 2. The 12-lead electrocardiogram on day 83 of treatment with fluconazole.

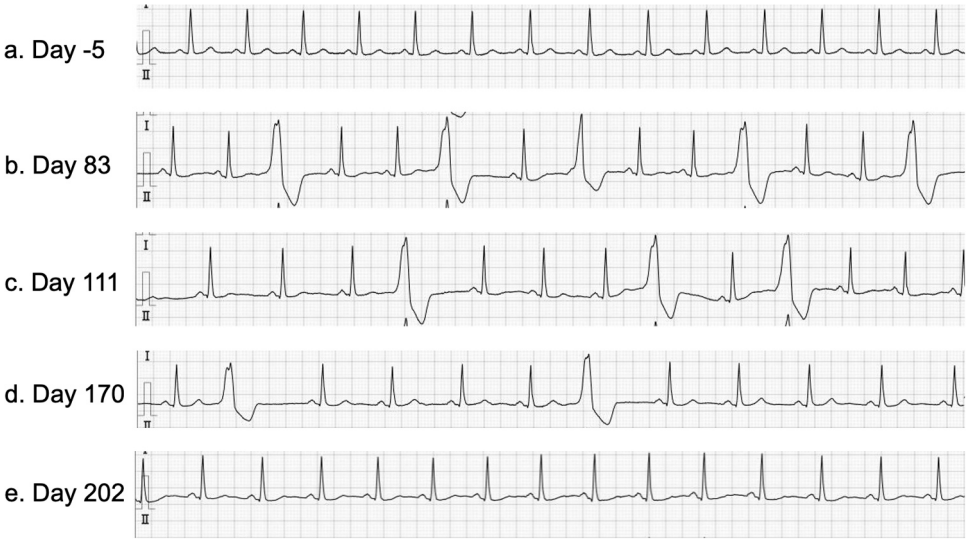

Fig. 3. Electrocardiogram findings during fluconazole treatment. The day of initiating fluconazole therapy was defined as day 0.

have been inducers of symptomatic PVCs in this case. Bictegravir, which was initiated before the onset of this case, was metabolized by UGT1A1 and CYP3A [13]. Thus, we believe that FLZ co-administration is unlikely to alter bictegravir exposure significantly. In addition, the serum concentration of FLZ is theoretically unaffected by administration of these drugs. Therefore, we concluded that the interaction between FLZ and other drugs had a limited effect on symptomatic PVCs in this case.

PVCs, which are generally considered mild and non-fatal arrhythmias, may be overlooked. Frequent PVCs are associated with fatal arrhythmias such as ventricular tachycardia and ventricular fibrillation [8]. Recently, even symptomless PVCs have been considered a cause of reversible cardiomyopathy [14]. Although it is acceptable to follow PVCs in low-risk patients without medical therapy or catheterization, treatments such as beta-blockers and catheter ablation may be used if PVCs persist for a long time without improvement [8]. In our case, the burden of PVCs per day was unknown because Holter ECG monitoring was not performed. Therefore, we determined that action to improve the PVCs should be taken, considering the uncertainty of the exact burden of PVCs. A standard intervention for drug-induced PVCs is discontinuation of the drug suspected of causing PVCs. However, we decided to reduce the dosage of FLZ and continue its use considering the following reasons: the impossibility of interrupting the treatment of pulmonary cryptococcosis and the fact that FLZ is the highest priority among oral antimicrobial agents effective against pulmonary cryptococcosis. As a result, the patient could complete six months of treatment for pulmonary cryptococcosis without any new cardiovascular events. Follow-up 12-lead ECGs allowed us to observe a decrease in the frequency of PVCs with the reduction of FLZ and the disappearance of PVCs with the discontinuation of FLZ. This case suggests that prior ECG evaluation and careful follow-up to detect the onset of any new arrhythmias are critical when drugs with potential cardiac side effects are used.

In this case, there were some limitations regarding the methods used for the evaluation of the patient's cardiovascular system. The exact frequency of PVCs per day is unknown because Holter ECG monitoring was not performed before or after FLZ administration. Moreover, echocardiography was not performed before or after FLZ administration. Thus, it was impossible to determine in depth how the PVCs which were persistent for a few months affected cardiac function. If cardiac function had been evaluated before FLZ administration, more appropriate follow-up could have been done when drug-induced electrocardiographic changes occurred. Despite these limitations, this case report is significant because we observed PVCs induced by FLZ with careful monitoring and 12-lead ECGs, which can be performed quickly and easily in most medical facilities.

Conclusions

We encountered a case of frequent PVCs without QT prolongation induced by FLZ alone during the treatment of HIV-related pulmonary cryptococcosis. Non-fatal arrhythmias associated with FLZ may be overlooked. Careful follow-up for new-onset arrhythmias and ECG evaluations before and after FLZ administration are essential.

Ethics approval and consent to participate

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Kazuhiko Nakaharai: Conceptualization, Writing – original draft, Writing – review & editing. **Kumi Tamura:** Conceptualization, Writing – original draft. **Masaki Yoshida:** Conceptualization, Project administration, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflicts of interest

All the authors have no competing interests.

Authors' contributions

T.K. and N.K. created the initial draft of the manuscript. All authors participated in collecting clinical data and approved the final version of the manuscript.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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