Case Report

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Cyclophosphamide-induced atrial fibrillation in the context of ANCA-associated vasculitis: a case report

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Introduction and importance: Cyclophosphamide is a widely used immunosuppressant for inducing remission in various immune-mediated conditions. However, its potential for cardiotoxicity is well documented. One of the earliest possible manifestations of this cardiotoxicity following cyclophosphamide infusion is atrial fibrillation (AF), which typically presents within 48 h of the infusion.
Case presentation: The authors present a case of a 58-year-old male with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis who presented to the emergency department with clinical features of acute kidney injury. Following subsequent assessment and evaluation, the patient was managed in the intensive care unit with hemodialysis and intravenous corticosteroids. He was aimed at inducing remission with cyclophosphamide infusion. However, a few hours following induction with cyclophosphamide infusion, the patient developed palpitation, sweating, and tachycardia with a heart rate of 140–180/min. The electrocardiogram showed an irregular QRS complex with an absent p-wave. AF was diagnosed and managed with amiodarone infusion for 24 h followed by oral maintenance dosing. No further episode of AF occurred following cessation of cyclophosphamide and switching to rituximab for the treatment of ANCA-associated vasculitis.
Clinical discussion: Cyclophosphamide, even at lower dosages, can cause cardiotoxicity in patients with renal impairment due to the delayed elimination of its toxic metabolites. In addition, patients who receive CYP 450 inducers, such as prednisone, may experience the accelerated build-up of its toxic metabolites, thereby raising the risk for cardiotoxicity.
Conclusion: The cardiotoxic manifestation of cyclophosphamide can arise from its use in several immune-mediated conditions. Given its potential for cardiotoxicity, careful cardiac monitoring during and after cyclophosphamide infusion is essential to ensure timely intervention, if needed.

Keywords: ANCA-associated vasculitis, atrial fibrillation, cardiotoxic, case report, cyclophosphamide

Introduction

Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) comprises a group of autoimmune illnesses that can cause significant systemic inflammation, predominantly affecting the small-sized blood vessels in various organs, potentially leading to organ failure[1]. Neutrophil activation in AAV causes the release of proteases, reactive oxygen species, and other pro-inflammatory mediators, impacting the vascular endothelium and contributing to the complex pathophysiology of the disease[2]. ANCA-associated vasculitis consists of microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, and granulomatosis with polyangiitis. AAV is frequently treated with the

HIGHLIGHTS

- Cyclophosphamide-induced cardiotoxicity ranges from a wide array of clinical presentations including atrial fibrillation to acute decompensated heart failure. Hence, vigilant assessment, monitoring, and timely treatment are warranted during such instances.
- Pathophysiology of cyclophosphamide-induced cardiotoxicity includes direct myocardial damage, oxidative stress from active metabolites of cyclophosphamide like phosphamide and acrolein, along with inflammatory cytokine dysregulation, highlighting the development of potential targets for prophylactic intervention in the future.
- Risk factors such as renal impairment, advancing age, cardiopulmonary comorbidities, and concurrent use of medication that induce the CYP450 enzyme leading to the potential build-up of active metabolites of cyclophosphamide such as high-dose corticosteroids, in this case, underscores the importance of promptly identifying such risk factors and necessitates subsequent personalized dosing strategies or other alternatives.

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immunosuppressant cyclophosphamide (CYC). It acts by cross-linking DNA strands, interfering with DNA replication and transcription, and ultimately causing activated immune cells to undergo apoptosis[3]. CYC has been found to lower disease activity, enhance organ function, and lower the chance of relapse[4]. CYC can cause various complications related to the hematological, gastrointestinal, and cardiovascular systems, including atrial fibrillation (AF).

AF is the most common cardiac arrhythmia routinely encountered in clinical practice, characterized by rapid and uncoordinated electrical activity in the atria resulting in the ineffective contraction of the atria and a decrease in cardiac output[5]. A recent meta-analysis has placed the risk of all cardiovascular events in AAV patients as being nearly 65% higher as compared with the general population[6]. Therefore, the likelihood of cardiac arrhythmias in these patients receiving CYC increases. Although the precise nature of how CYC induces AF is yet to be fully understood, one potential mechanism is the direct toxicity of CYC in the cardiac muscles, which can result in cardiac remodeling and myocardial fibrosis leading to aberrant electrical conduction[7].

Case presentation

A 58-year-old male presented to the emergency department with complaints of shortness of breath for the last 4–5 days and decreased urine output for 3 days. Shortness of breath was gradual on onset and was associated with orthopnea. Decreased urine output was accompanied by gross hematuria throughout the urinary stream. He reported malaise and anorexia as well. A review of his past medical history revealed hypertension and chronic obstructive lung disease (COPD) with cor-pulmonale. He was an ex-smoker with more than 30 pack years of smoking history. He occasionally drank alcohol but denied using illicit drugs. He also denied having fever, abdominal pain, chest pain, weight loss, night sweats, hematemesis, melena, other genitourinary symptoms, tuberculosis exposure, any recent travel history, or a history of coagulopathy. The medication history included amlodipine and atenolol for hypertension for the past 10 years, which was well controlled, and a formoterol-tiotropium bromide inhaler for COPD for the last 5 years. The patient did not have any COPD exacerbations in the past. The patient had no significant past surgical history, and the family history was unremarkable. In addition, the patient did not have any prior episodes of AF or other arrhythmias.

On physical examination, he had a blood pressure of 170/100 mmHg, heart rate of 110/min, SpO2 of 82% in room air, and respiratory rate of 28 breaths/min. On further examination, pallor and edema were noted and he was in respiratory distress. Bilaterally decreased air entry along with bibasilar crackles were heard on chest auscultation.

At the time of presentation, his laboratories were significant for blood urea nitrogen at 95.3 mg/dl and creatinine at 8.1 mg/dl with an estimated glomerular filtration rate (eGFR) of 8.23 mL/min/1.73 m^2. Na was 130, K was 5.3, and Hb was 10.1 g/dl. Blood gas analysis showed a pH of 7.31, a pO_2 of 87, a pCO_2 of 28, an HCO_3 of 14.1, a lactate level of 0.8, and an anion gap of 12 mmol/l. Procalcitonin, leukocyte counts, and liver enzymes were normal. Urinalysis showed red blood cells (RBCs) > 100/hpf. Urine sediment was positive for dysmorphic RBCs. Chest X-ray showed emphysematous changes in the lungs, increased cardiac silhouette size, and batwing opacities. There was no focal consolidation. An electrocardiogram (EKG) showed sinus tachycardia. Transthoracic echocardiography was unremarkable except for distended non-collapsible inferior venacava at 28 mm. A plain computed tomography scan of the chest showed diffuse ground glass opacities, interlobular septal thickening, bilateral minimal pleural effusion, and central cylindrical bronchiectasis with emphysematous changes. He was admitted to the ICU for further evaluation and management. Subsequent evaluation and investigation revealed a persistently high serum creatinine, borderline high c4 at 43.8 mg/dl (Ref. 9–36 mg/dl), and normal c3. Antinuclear antibody, anti-glomerular basement membrane, and proteinase 3-specific anti-neutrophil cytoplasmic antibody were negative. However, myeloperoxidase-specific anti-neutrophil cytoplasmic antibody was significantly positive at >300 U/ml (Ref: Negative < 12 U/ml). The diagnosis of ANCA-associated vasculitis leading to acute kidney injury (AKI) was made, and CYC infusion was planned for remission. Hemodialysis was performed on three separate occasions during his stay at the hospital, and his pulmonary edema resolved after the first dialysis session. The patient was also treated with IV methylprednisolone pulse therapy for 3 days followed by oral prednisone.

CYC infusion was administered 24 h after the completion of the second cycle of hemodialysis. CYC 1 gm in 250 ml of normal saline was started slowly over 2 h. Subsequently, 90 min after completing the CYC infusion, the patient developed palpitations, sweating, and tachycardia with a heart rate of 140–180/min in telemetry. EKG showed tachycardia with a rate of 152 with irregular QRS complexes with an absent p-wave due to AF with rapid ventricular rate as shown in the figure below. AF was managed with IV amiodarone 150 mg in 100 ml Dextrose 5% bolus over 15 min, followed by 1 mg/min infusion over 6 h and 0.5 mg/min infusion over 18 h. The patient reverted to sinus rhythm after 10 min of amiodarone infusion. Oral Amiodarone was overlapped with the last 6 h of infusion, and oral metoprolol was added for rate control. His AF improved afterward, and, during the rest of his hospital stay, the patient did not develop another episode of AF. The patient's ANCA-associated vasculitis with AKI leading to end-stage renal disease is being managed with maintenance hemodialysis and IV rituximab. A renal biopsy was planned following the stabilization of the patient's condition. An echocardiogram repeated before discharge remained unchanged from his previous echocardiogram.

The diagnosis of CYC-induced AF was made based on the associated onset of symptoms following CYC usage and the lack of recurrence of AF following CYC discontinuation.

Case discussion

Cyclophosphamide is an extensively used immunosuppressive agent for treating malignancies, immune-mediated glomerulonephritis, and ANCA-associated vasculitis[8]. Although progress has been made in therapeutic modalities for the treatment of autoimmune diseases, resulting in subsequent improvements in mortality and morbidity, life-threatening toxicities such as immunosuppressant-induced cardiotoxicity remain a challenging problem. These cardiac complications can range from isolated instances of tachyarrhythmias such as AF or supraventricular arrhythmia to ventricular arrhythmias[7,9]. Additionally, manifestations may include pericarditis, restrictive cardiomyopathy, and, in severe cases, cardiac tamponade or fulminant cardiac failure[10].

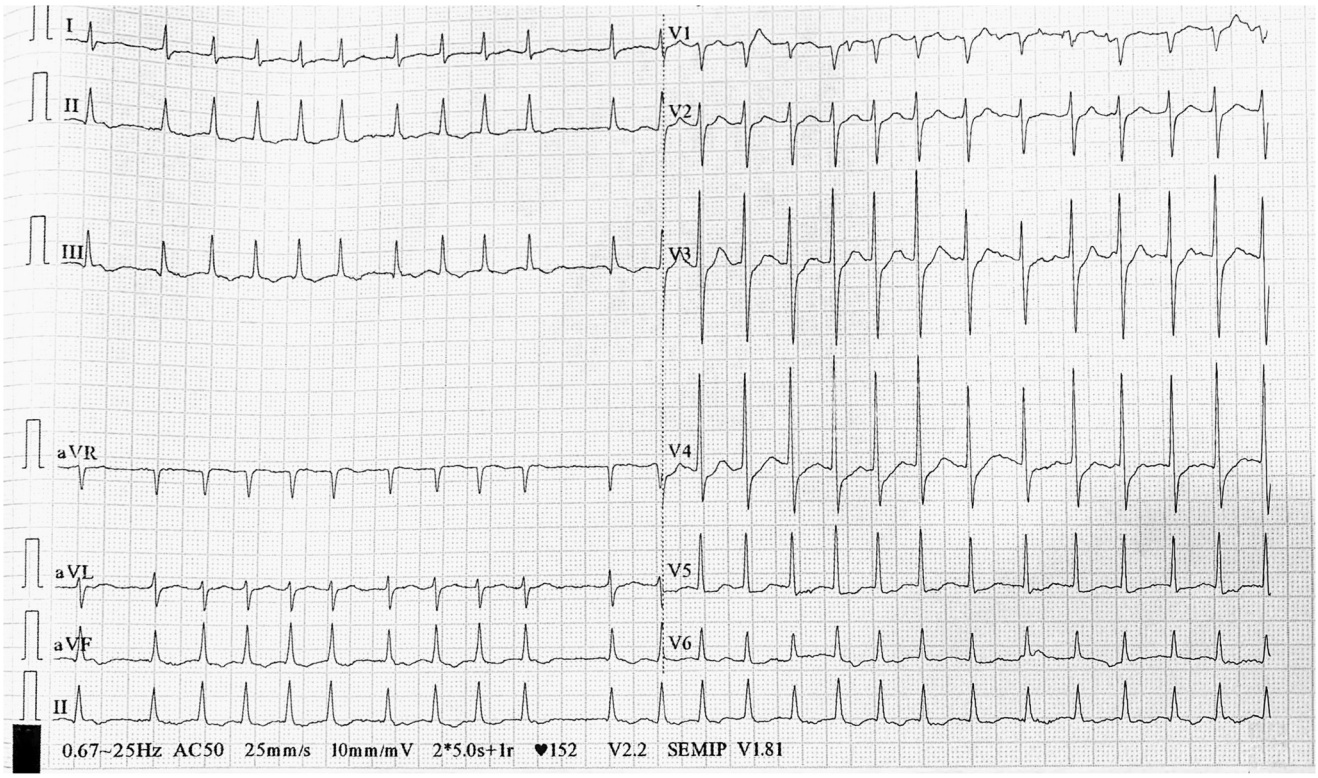

Figure Electrocardiogram (EKG) showing atrial fibrillation with a rapid ventricular rate.

Although the exact mechanism of CYC-induced cardiac toxicity is still not fully understood, the main predominant mechanism includes direct myocardial and free radical damage from its metabolite, phosphamide. This process leads to endothelial and myocyte injury, ultimately resulting in the leakage of toxic metabolites and proteins[11]. CYC has been documented to trigger the production of tumor necrosis factor- alpha (TNF-α) and Interleukin (IL-1β), while concurrently decreasing IL-10 expression. These actions contribute to myocardial hypertrophy, fibrosis, and interstitial hemorrhage, induce apoptosis of myocardial cells, and result in a pro-arrhythmogenic state, promoting AF development[11].

In recent decades, there has been a growing interest in studying the pharmacokinetics of CYC. It is known that CYC is a prodrug that needs activation by cytochrome P450 enzymes, leading to the production of 4-hydroperoxy-cyclophosphamide and aldophosphamide. These compounds then undergo β elimination to generate phosphamide and acrolein, which are also considered to be cardiotoxic[11]. CYC metabolism occurs in the liver, and its metabolites are eliminated by the kidneys. Therefore, patients with renal insufficiency, like this patient diagnosed with AAV resulting in AKI, are at an increased risk of CYC-related cardiac toxicity even at regular doses. Consequently, dose adjustments of CYC should be implemented to prevent its side effects in these susceptible individuals. Goldberg and colleagues proposed a threshold dose of around 1.5 g/m^2[12]. In this case, the patient developed AKI due to AAV, which did not improve until he underwent hemodialysis. Following the completion of the second cycle of hemodialysis, a CYC infusion of 600 mg/m^2 was administered, which induced AF with a rapid ventricular rate in this patient, which was significantly below the proposed critical threshold[12].

Several independent risk factors have also been identified to increase the risk of CYC-related cardiotoxicity, which notably includes advanced age and the presence of malignancy[13]. Moreover, low ejection fraction (EF < 50%), prior radiation exposure to the mediastinum, and prior use of other cardiotoxic agents also increase the risk of cardiotoxicity in patients receiving CYC treatment, none of which were present in the patient. Research indicates that steroids such as prednisone and dexamethasone are known to induce the P450 enzyme[7]. In this scenario, the patient's medical history of COPD and the administration of prednisone at a dosage of 60 mg for at least 5 days likely triggered the P450 enzyme, leading to the accelerated build-up of toxic metabolites of CYC and contributing to an increase in the risk of cardiotoxicity.

The symptoms of cardiotoxicity related to CYC vary in severity and presentation, depending on the specific pathology affected by CYC and the associated risk factors. Associated risk factors that can precipitate CYC-induced cardiotoxicity include decompensated heart failure with low EF and uncontrolled hypertension at the time of infusion, neither of which were present in this patient. Typically, tachyarrhythmia such as AF becomes evident within 48 h after the initial dose[10]. Detecting cardiotoxicity related to CYC early on is crucial, particularly in patients with low eGFR, as it can lead to rapidly worsening heart problems. Careful telemetry monitoring during and after the infusion of cyclophosphamide (CYC) is essential for detecting any arrhythmias. If detected, the initial assessment typically involves a 12-lead EKG to identify any tachyarrhythmia caused by the chemotherapy. Although the EKG helps rule out arrhythmias, an echocardiogram is necessary to measure the left ventricular ejection fraction (LVEF) and exclude

potential heart failure. However, tachyarrhythmia might obscure the assessment of cardiac chambers, and a decrease in LVEF might not manifest immediately[9]. Heart failure indicators such as B-type natriuretic peptide can serve to exclude acute cardiac failure, particularly in cases of high-dose administration[9]. Moreover, cardiac magnetic resonance imaging can be employed to identify changes in the structure of heart chambers when high doses of CYC are administered[14].

The treatment approach for CYC-induced AF should be tailored to each individual. If there are any indications of cardiotoxicity related to CYC, whether observed clinically or through laboratory findings, the first and most critical action is to discontinue the medication promptly. Once identified, management of tachyarrhythmia follows the standard approach, with medical interventions aimed at controlling heart rate and rhythm in hemodynamically stable patients. In instances where arrhythmias persist despite medical management or when patients are hemodynamically unstable, it is crucial to swiftly identify the situation and provide robust hemodynamic assistance with cardioversion[15].

Conclusion

This case report underscores the importance of being vigilant and watchful for potential cardiotoxic manifestations like AF in patients receiving cyclophosphamide, especially those with pre-existing cardiopulmonary comorbidities and deranged renal function. Clinicians should be wary of this manifestation of cyclophosphamide and manage it firstly by promptly discontinuing the drugs and then timely starting appropriate anti-arrhythmic agents tailored to individual patient's needs. Pre-treatment with steroids such as prednisone, as in this case can induce the CYP 450 enzyme, which accelerates the build-up of active metabolites of cyclophosphamide leading to potential cardiotoxic manifestation. Further studies are warranted to understand better the incidence, mechanisms, and prevention of cyclophosphamide-induced arrhythmias.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Author contribution

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