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Rituximab-Induced Acute ST Elevation Myocardial Infarction

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Background: Rituximab has rarely been associated with acute coronary syndrome (ACS). We report the case of a patient in whom rituximab, a monoclonal antibody used to treat lymphomas of B-cell origin, induced ST elevation myocardial infarction.
Case Report: A 46-year-old male patient diagnosed with stage II non-Hodgkin lymphoma presented to the emergency department with acute crushing, substernal chest pain that radiated to his back 1 day after a chemotherapy infusion with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. An electrocardiogram revealed normal sinus rhythm with ST elevations in the inferior leads. The patient underwent primary percutaneous coronary intervention (PCI) of his right coronary artery and first diagonal artery with placement of drug-eluting stents. He did well postprocedure and resumed therapy with rituximab under close monitoring by the cardiology and oncology departments without any further cardiac events.
Conclusion: In patients with ACS because of chemotherapy, complete revascularization during PCI should be considered.

Keywords: *Acute coronary syndrome, lymphoma–non-Hodgkin, myocardial infarction, percutaneous coronary intervention, rituximab*

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INTRODUCTION

Chemotherapy-induced cardiovascular complications include myocardial dysfunction, conduction abnormalities, hypertension, venous thrombosis, and myocardial infarction.[1] Myocardial infarction has a high risk of being life threatening, although the incidence after chemotherapy remains low at 1%-5%.[1] Rituximab, a monoclonal antibody used to treat lymphomas of B-cell origin, may be associated with acute coronary syndrome (ACS), although few cases have been reported in the literature.[2,3] We report the case of a male patient with a diagnosis of non-Hodgkin lymphoma who developed an acute ST elevation myocardial infarction (STEMI) after administration of chemotherapy with rituximab infusions.

CASE REPORT

A 46-year-old man with a medical history of tobacco use and a recent diagnosis of stage II diffuse large B-cell lymphoma of germ cell origin presented to the emergency department with a chief complaint of dyspnea and chest discomfort approximately 10 hours after his initial dose of chemotherapy at the infusion center. He had received a rituximab infusion as part of his rituximab, cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone (R-CHOP) chemotherapy regimen the day prior to presentation. During his initial chemotherapy treatment, he felt anxious and noted difficulty swallowing. He was treated with diphenhydramine and hydrocortisone that relieved his symptoms, and the infusion was completed. During the infusion, his vital signs were within normal limits.

The following day, he presented to the ambulatory infusion center for a second round of rituximab infusion. Approximately halfway through this infusion, he began to experience mild dyspnea and chest discomfort. The infusion was stopped, and the patient was discharged home with instructions to go to the emergency department if his symptoms did not improve or worsened. After initially feeling better, the patient experienced crushing substernal chest pain. He presented to the emergency department where he described the pain as an ''achy pressure'' that was constant, was 5 of 10 in severity, and radiated to his back.

The patient's only known cardiovascular risk factor was a 25 pack-year smoking history with cessation for the last 2 weeks. He had no other known cardiovascular risk factors such as diabetes mellitus, hyperlipidemia, hypertension, or a family history of coronary artery disease. Prior to chemotherapy, an echocardiogram demonstrated a normal ejection fraction of 65% with no evidence of valve disease or wall motion abnormalities. His vital signs during presentation to the emergency department were blood pressure 133/63 mmHg, pulse 95 bpm, temperature 36.7°C, and oxygen saturation 98% on room air. His electrocardiogram

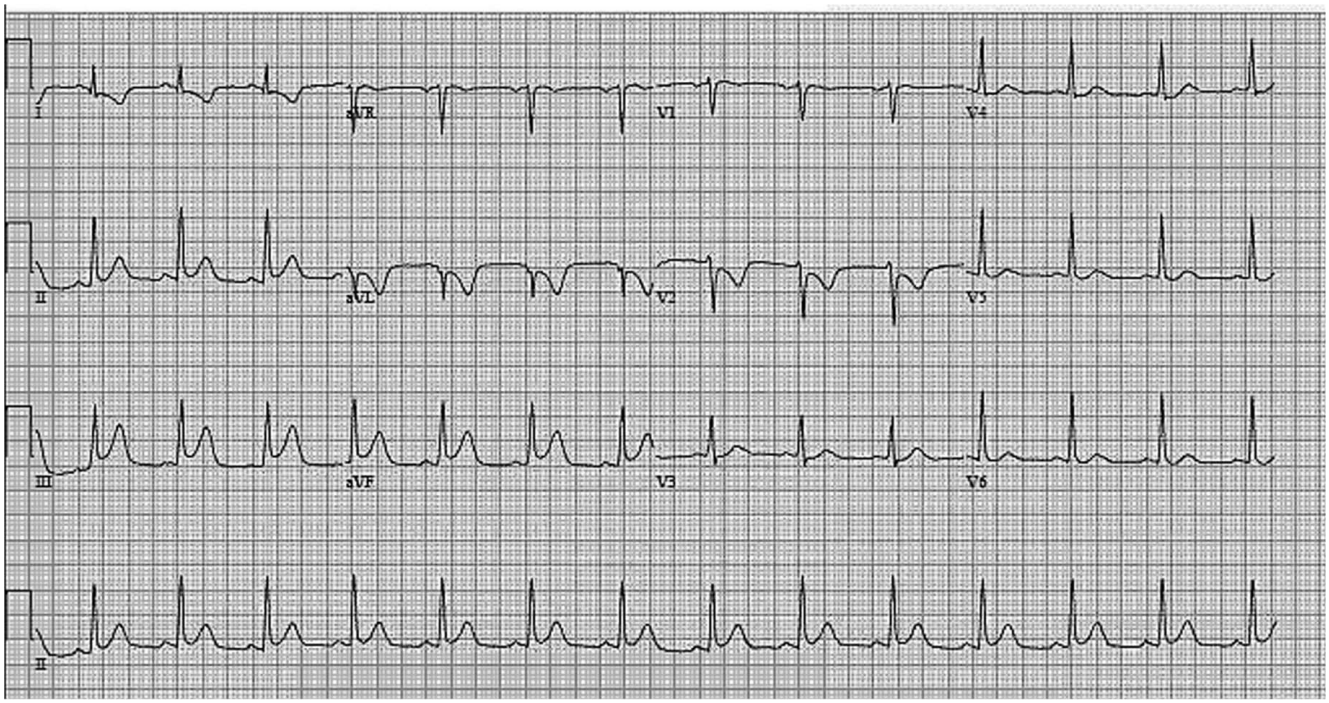

Figure 1. Electrocardiogram demonstrating ST segment elevation in the inferior leads (leads II, III, and aVF) with reciprocal T wave inversion in lateral leads (leads I and aVL).

showed normal sinus rhythm with ST elevations in the inferior leads (II, III, and aVF) concerning for an inferior infarct (Figure 1), and laboratory work was significant for elevated cardiac biomarkers (troponin I 0.044 ng/mL). The patient was taken urgently to the catheterization laboratory for angiography. During cardiac catheterization, occlusion of the proximal right coronary artery with thrombolysis in myocardial infarction (TIMI) grade flow 0 and 80% stenosis of the first diagonal artery with TIMI grade flow 3 were noted (Figure 2A). Both lesions were successfully treated with placement of drug-eluting stents with no residual stenosis and postintervention TIMI grade flow 3 (Figure 2B).

Since his coronary intervention, the patient has been followed in the cardiology and oncology clinics, and he has completed 3 additional rounds of chemotherapy infusion including rituximab. Despite treatment with R-CHOP, he had progression of his lymphoma and was switched to rituximab, etoposide, prednisone, vincristine (Oncovin), cyclophosphamide, and hydroxydaunorubicin for treatment of his aggressive diffuse large B-cell non-Hodgkin lymphoma. The patient continued to be compliant with dual antiplatelet therapy for his drug-eluting stents, and his post–myocardial infarction echocardiogram demonstrated normal left ventricular function with no wall motion abnormalities. He has had no further cardiac issues.

DISCUSSION

Many chemotherapeutic agents are associated with ACS, including taxanes, vinca alkaloids, 5-fluorouracil, cisplatin, carboplatin, bevacizumab, sorafenib, and erlotinib.[1] Rituximab, however, most commonly causes cardiac arrhythmias, and its reported rate of ACS is $<0.1\%$.[2] To our knowledge, our case is only the third report in the literature of rituximab-induced STEMI.

Rituximab is a human monoclonal antibody that binds CD20 receptors and is expressed on B-cell–mediated non-Hodgkin lymphomas.[4] The most common severe side effect associated with rituximab is immediate hypersensitivity reactions that are type I reactions involving immunoglobulin E–mediated release of histamine and other mediators from mast cells and basophils. However, more serious complications such as hepatitis reactivation, bowel perforation, progressive multifocal encephalopathy, and cardiac arrhythmias or ischemia have also been documented.[4] The mechanism of ACS associated with rituximab is unknown but is hypothesized to be a cytokine-mediated reaction that eventually causes rupture of atherosclerotic plaque.[2]

In the case presented here, the patient's male gender and smoking history increased his risk of coronary artery disease. Additionally, the use of vincristine, which has been associated with myocardial infarction through induced cell-cycle arrest of cardiac endothelial cells, may have increased his risk of ACS.[5-7] The rituximab appears to have caused plaque rupture, leading to our patient's presentation with STEMI. He was treated appropriately with percutaneous coronary intervention (PCI) to his right coronary artery, a potentially lifesaving measure. Additionally, he underwent PCI to the 80% stenosis in his first diagonal artery. PCI of the right coronary artery, which was the culprit lesion, and of the significant stenosis in the first diagonal artery was pursued because of the patient's need for further rituximab therapy.

Traditionally, a method of staged multivessel PCI is used in which only the culprit lesion is treated at the time of the acute STEMI and other significant lesions are treated in approximately 1 month.[8] Evidence, however, supports that complete revascularization at the time of a STEMI leads to improved short- and long-term survival vs the staged

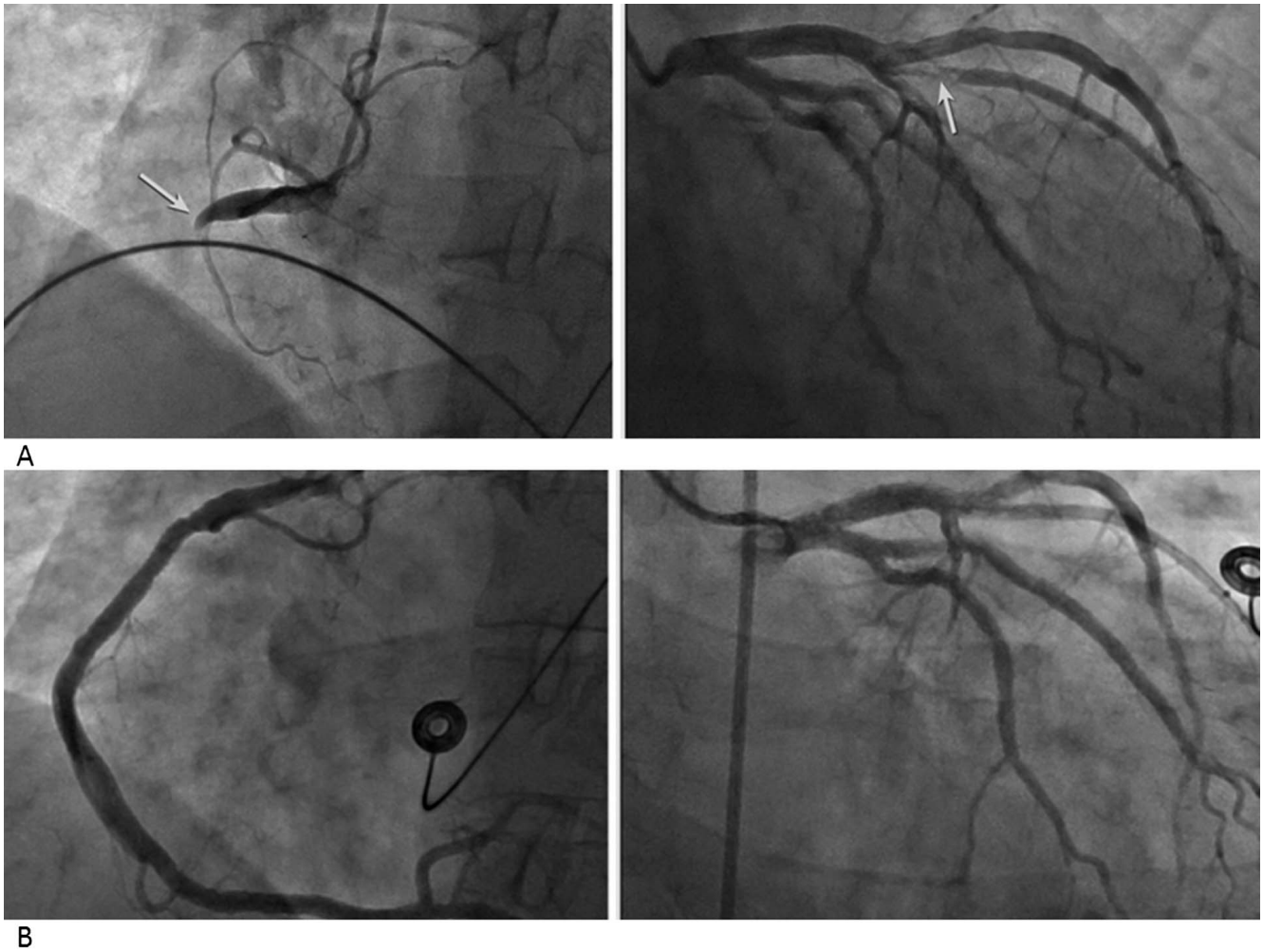

Figure 2. A: Angiogram of the right coronary artery preintervention (left frame) and the first diagonal artery preintervention (right frame). Arrows denote the areas of stenosis. B: Angiogram of the right coronary artery after percutaneous coronary intervention (left frame) and the first diagonal artery after percutaneous coronary intervention (right frame).

approach.[9] Our patient had no further episodes of ACS after his complete revascularization despite ongoing treatment with rituximab. Therefore, in high-risk patients who present with rituximab-induced ACS, a complete revascularization may be warranted at the time of the initial angiogram, but further research is needed to routinely suggest this approach.

Our case demonstrates ACS in a patient immediately after receiving rituximab infusion for non-Hodgkin lymphoma, a rare but potentially fatal complication associated with chemotherapy infusion. After complete revascularization of all lesions at the time of the patient's STEMI, he was able to continue chemotherapy treatment under the guidance of a comprehensive multidisciplinary approach between cardiology and oncology. While further studies are needed to better understand the effects of rituximab and ACS, along with the potential benefits of complete revascularization at the time of intervention, we recommend a collaborative approach to treat these complicated patients.

CONCLUSION

In individuals with ACS because of chemotherapy, complete revascularization PCI should be considered.

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