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Delayed Myocardial Infarction Associated With Rituximab Infusion: A Case Report and Literature Review

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To report a case of delayed myocardial infraction after rituximab infusion. A 52-year-old woman with history of refractory idiopathic thrombocytopenic purpura had hypertension, seizure, and mild coronary artery disease and received rituximab; after 24 hours, she returned back with chest pain, nausea, and vomiting. Her electrocardiogram showed a ST-elevation in the II, III, aVF, and aVR lead and ST depression in I and aVL lead; after another complementary test, the myocardial infraction was confirmed. The patient was sent to the intensive care unit, and after 8-day hospitalization, she was discharged. Based on the Naranjo Probability Scale, the likelihood of rituximab-induced acute myocardial infarction in this case was probable. Rituximab is generally well tolerated; however, cardiovascular effects of this drug can be fatal. The side effects usually occur during or a short time after infusion; this case demonstrated that rituximab side effects may occur with delay. This case demonstrates, although a rare phenomenon, myocardial infraction may occur after 24 hours and clinicians should be aware of this fatal effect even after a period of time in patients receiving rituximab, especially in patients with history of coronary artery disease.

Keywords: acute myocardial infarction, cardiotoxicity, ITP, rituximab

INTRODUCTION

Around 10 years ago, researchers introduced rituximab as an alternative treatment for patients with chronic idiopathic thrombocytopenic purpura (ITP) on the failure of initial glucocorticoid treatment. It is useful in about 40% of patients with ITP.[1] Rituximab may lead to platelet destruction.[2] Introduction of new therapies and late remission after splenectomy in patients with ITP have resulted in avoiding or deferring splenectomy, which can decrease the rate of splenectomy around 20%–25% in recent years.[3] Approximately 80% of patients may experience an infusion-related reaction, ranging from mild reactions including fever, chills, and rigors to severe reactions such as hypoxia, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation (VF), or cardiogenic shock with the first dose. Myocardial infarction after rituximab or other monoclonal antibody therapies is rare. Patients with known cardiac risk factors, inflammatory or lymphoproliferative disorder, or concomitant corticosteroid treatment face highest risk for myocardial infarction complication. Vasoconstriction, platelet activation, and rupture of atherosclerotic plaque are due to cytokine release after rituximab infusion, resulting in acute coronary syndrome.[4] This study represents the first reported case of acute coronary syndrome in a patient with ITP 1 day after rituximab administration.

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The authors have no conflicts of interest to declare.

Authors' note: The patient consented to the publication of this case report.

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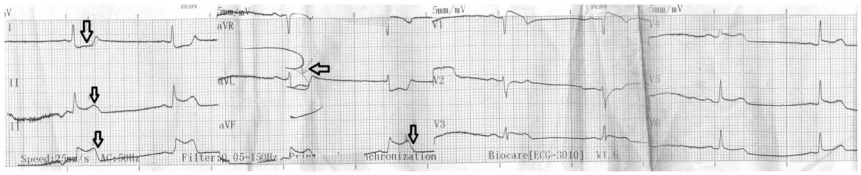

FIGURE 1. Changes related to STEMI. Electrocardiogram (ECG), note the extensive ST-segment depression in I and aVL lead, which are the lateral ECG leads, and ST-segment elevation in leads II, III, and aVF, indicating an inferior wall acute myocardial infarction.

CASE REPORT

We present a 52-year-old woman as a known case of ITP. She had a history of hypertension, seizure, and also had a coronary arteriography 2 years before, with diagnosis of mild coronary artery disease (CAD). She had a history of appendicitis and appendectomy. Her medications were enalapril 20 mg twice a day, metoprolol 25 mg twice a day, hydrochlorothiazide 25 mg once a day, and prazosin 1 mg twice a day. This patient was a refractory case to prednisolone and IVIG. Rituximab treatment was considered after failure of several long-term and high-dose immunosuppressive therapies (prednisolone 50 mg once a day). Her physician decided to start rituximab for her in accordance with persistent severe thrombocytopenia (platelet count was 10,000/μL) after 2 weeks of prednisolone therapy. The patient received rituximab 375 mg/m^2 (600 mg) diluted in 500 mL 5% dextrose in water solution infused over 5 hours. She premedicated before rituximab infusion as followed by 1 g oral acetaminophen 1 hour before infusion, 10 mg IV chlorpheniramine, 8 mg dexamethasone, and 100 mg ranitidine. No infusion reactions were seen on day 1. One day after the first infusion, the patient experienced mild chest pain, nausea, and vomiting. Urgent electrocardiogram showed an ST-elevation in the II, III, aVF, and aVR lead and ST depression in I and aVL lead after the first chest pain (Figures 1, 2). The cardiac troponin I (cTnI) level was at 14.95 ng/mL (normal range up to 5 ng/mL), creatine kinase (CPK) concentration was at 241 IU/L (normal range in female ≤149), and CPK-MB of 39 IU/mL (normal range up to 6% total CPK or less than 25). After myocardial infarction, the ventricular tachycardia and VF occurred and followed by seizure. The condition of patient was reversed by the electric discharge from a defibrillator and shock. Then, the patient shifted to intensive care unit and she was intubated and received amiodarone 1 mg/min for 6 hours and then 0.5 mg/min for 18 hours. Also, she received phenytoin 100 mg twice daily and then converted to sodium valproate based on neurology consult. Repeated electrocardiogram 40 minutes after symptom onset showed a sinus tachycardia amd ST depression in v4 and v6 lead (Figures 3, 4). Transthoracic echocardiogram was performed for the patient and ejection fraction estimated by 50% without other abnormalities. Cholesterol levels were slightly elevated (total and LDL cholesterol levels were 250 and 105, respectively, and triglycerides 167 mg/dL). After 2 days in the intensive care unit, the patient was sent to coronary care unit and she candidated for coronary angiography, but the angiography could not be performed for the patient because of her low platelet count. After 4 days in coronary care unit, the patient went to a cardiovascular unit with medicine orders of diltiazem 30 mg 3 times a day, enalapril 20 mg/d, and hydrochlorothiazide 12.5 mg daily. The patient was discharged in a stabilized condition with platelet count of 28,000 and prednisolone 50 mg/d after 8-day hospitalization.

DISCUSSION

We report the case of delayed acute myocardial infarction associated with rituximab in a known case of ITP. Based on the Naranjo Probability Scale, the likelihood of rituximab causing myocardial infarction in this case

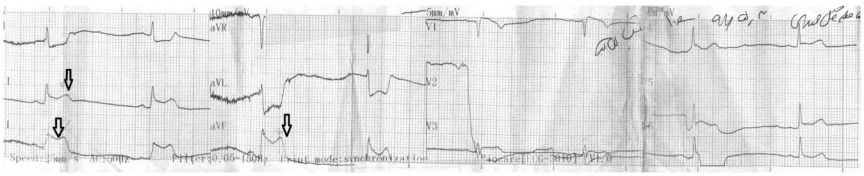

FIGURE 2. Electrocardiogram showing ST-elevation myocardial infarction in leads II, III, and aVF.

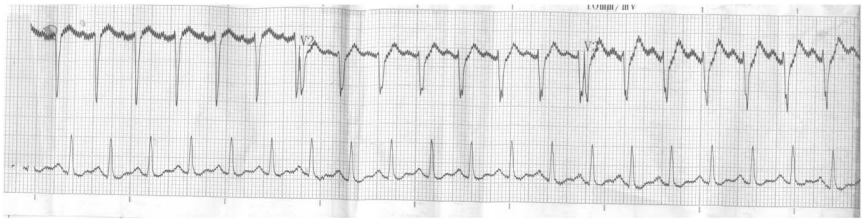

FIGURE 3. Repeated ECG, 40 minutes after symptom onset, showing a sinus tachycardia.

is probable. This scale is a questionnaire to determine the likelihood of whether an adverse drug reaction is actually due to the drug rather than the other factors.[5] Rituximab is a humanized monoclonal antibody targeting the CD20 determinant on B cells. It was used initially for the treatment of malignant lymphoma. It is therefore used in autoantibody-mediated disorders therapy. Promising results by rituximab in patients with ITP were observed in several case reports and uncontrolled studies. A systematic review of reports on rituximab use in adults with chronic ITP was performed by Arnold et al.[1] They observed a complete response, usually 3–8 weeks after the first infusion in 46% of patients.[1,6–8] Rituximab is now commonly used to manage chronic refractory ITP in Europe and North America, and it is strongly suggested before splenectomy.[9] Approximately 80% of patients receiving rituximab may experience an infusion-related reaction from fever, chills, and rigors to severe reactions (7%) characterized by hypoxia, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, VF, or cardiogenic shock with the first dose. Approximately 40% of patients receiving rituximab experience infusion-related reactions with subsequent infusion (5%–10% severe).[10] It has been seen that infusion reactions with humanized monoclonal antibodies typically occur within 30 minutes to 2 hours after the initiation of infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10 and 30% occur during subsequent treatments.[11] Premedication reduced frequency and intensity of the first infusion adverse effect. In such a case, the risk of fatal infusion reactions is higher with high baseline CD20-positive B lymphocyte load.[12,13] In another study, it has been suggested that the majority of these infusion reactions are thought to be related to interaction between rituximab and CD20, resulting in cytokine release from these cells.[14] Cardiovascular toxicity occurred in 8% of patients treated with rituximab for lymphoma cardiac in the form of dysrhythmias. It is suggested that the release of cytokines, such as interleukin-6 and tumor necrosis factor-alpha, can lead to arrhythmias.[15] Myocardial infarction is one of the fatal infusion reactions reported with rituximab in 2 case reports. Acute coronary syndrome after rituximab infusion may be due to the release of cytokines, which cause vasoconstriction, platelet activation, and/or rupture of atherosclerotic plaque.[16] In a case that has been previously recorded, the patient was a man of 60 with underlying disease of diabetes. It is likely that the patient had a preexisting vulnerable plaque. After initiation of rituximab infusion, the vulnerable plaque is due to release of cytokines spontaneously ruptured and resulting in acute total occlusion and myocardial infarction. This study concluded that vulnerable plaque rupture in patients with risk factors including CAD may be occurred.[17] In one other study, 3 patients experienced acute coronary syndrome after rituximab infusion. One of them had a known atherosclerotic heart disease, and the others had risk factors for CAD. Acute coronary syndromes can be associated with the infusion of rituximab. They recorded that patients receiving rituximab infusion and have an underlying disorder of CAD or CAD risk factors should be observed closely for signs of myocardial ischemia.[4] Myocardial infraction has been reported for a 52-year-old man treated for seronegative myasthenia

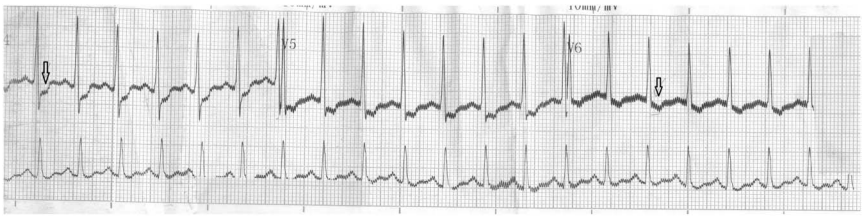

FIGURE 4. Repeated ECG, 40 minutes after symptom onset, showing a ST depression in v4 and v6 lead.

Table 1. Myocardial infarction and one case of cardiogenic shock after infusion of rituximab.

Diagnosis	Age	Sex	Onset of myocardial infraction	References	Underlying disease
Splenic lymphoma with villous lymphocytes	65	M	Few minutes after infusion	Gogia et al[19]	No
Chronic lymphocytic leukemia	58	M	During infusion	Armitage et al[4]	No
Burkitt-like lymphoma	61	M	During infusion	Armitage et al[4]	No
Burkitt-like lymphoma	72	M	Few minutes after infusion	Armitage et al[4]	Previous CAD
Diffuse large B-cell lymphoma	60	M	15 min after infusion	Arunprasath et al[17]	Diabetes
Seronegative myasthenia	52	M	10 h after third infusion	Renard et al[18]	No
Rheumatoid arthritis	70	F	6 mo after the first dose and 2 mo after the second one	van Sijl et al[20]	Past inferoposterior myocardial infraction, hypothyroidism
Rheumatoid arthritis	76	F	1 mo after the second dose	van Sijl et al[20]	No
Thrombotic thrombocytopenia purpura	20	F	After infusion	Millward[21]	No
Idiopathic thrombocytopenia purpurea	52	F	24 h after infusion	This case	Previous CAD

CAD, coronary artery disease.

and also a male patient with lymphoma too.[18,19] However, myocardial infraction has been seen in patients treated for rheumatoid arthritis.[20] In another case report, a fetal and severe infusion reaction including cardiogenic shock (ejection fraction 5%–10%) was occurred after the rituximab infusion in a patient with thrombotic thrombocytopenia purpura.[21] A summary of all cases are shown in Table 1. Because cardiovascular complications are disturbing for both cardiologists and oncologists, this adverse reaction may have an influence on patient outcomes. Moreover, patients with underlying heart disease are at most risk for cardiac events. The patient in this case had risk factor of underlying CAD. It seems that after release of cytokines in patients receiving rituximab, plaque rupture may occur in preexisting patients with CAD.

CONCLUSIONS

The present case indicates that unpredictable cardiovascular complications due to chemotherapy may have significant consequences on patient outcomes. We have considered that rituximab may have a disturbing effect on the cardiovascular system. To maximize both quality of life and survival, close observing of high-risk subset of patients before starting the rituximab therapy by both cardiologists and oncologists with the aim of balancing the risks of cardiotoxicity may be necessary. As a result, patients with a history of cardiac disease should be admitted and observed longer after rituximab administration.

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