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# Fatal myocardial infarction due to rituximab in the treatment of IgG4 related disease-another case, tip of the iceberg?

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## Abstract

Rituximab is being utilized off-label by physicians for many diseases such as myasthenia gravis, multiple sclerosis, CIDP, and Ig4 related disease such as Idiopathic Hypertrophic Pachymeningitis. Our case illustrates the danger of giving rituximab to an older person who may harbor asymptomatic coronary artery disease and incurring an arrhythmia or myocardial infarction from cytokine release. Our case along with the PI warning of rituximab and numerous other case reports should prompt physicians to obtain cardiology consultation prior to giving rituximab to an older population.

**Keywords**: Rituximab, cytokine release syndrome, myocardial infarction

## Introduction

Rituximab is a monoclonal immunoglobulin that binds to the CD20 on the surface of normal and malignant B-lymphocytes producing a substantial reduction of circulating B-lymphocytes. Numerous adverse effects are described in the prescribing information for health care professionals including cardiac arrhythmia and myocardial infarction. It is approved by the FDA for the treatment of non-Hodgkin lymphoma, CD20-positive chronic lymphocytic leukemia, rheumatoid arthritis, Wegener granulomatosis, and microangiopathic vasculitis. It is also used off-label for other diseases including neurological disorders such as myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, and idiopathic hypertrophic pachymeningitis (IHPM) which is a rare disorder that can be confined to the meninges or as part of a systemic disease called IgG4-related disease (Ig4-RD). Proposed pathogenesis is a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, often but not always, elevated serum IgG4 concentrations and molecular mimicry of microbial antigens and an allergic disorder. The response to immunosuppressives supports these proposals [1,2].

We report a case of a 78-year-old female who presented with persistent headache, dizziness, and tinnitus. Past medical history included long standing depression on sertraline, quetiapine, and valproate and 1 year ago underwent successful cervical laminectomy for cervical spondylosis without postoperative neurological deficit. Neurological examination and neurotology evaluation were normal. Gadolinium enhanced magnetic resonance imaging (MRI) brain revealed thickened enhancing meninges consistent with IHPM. Magnetic resonance angiogram of the brain was normal. Spinal fluid analysis, antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate and MRI of the cervical and thoracic regions were unremarkable. Computed tomography of chest, abdomen, and pelvis were negative. Positron emission tomography revealed increased uptake in the submandibular glands. Ophthalmology examination was normal.

Initial trial of high dose intravenous steroids with prolonged oral steroid taper failed. Clinical remission and complete normalization of brain MRI was achieved with subsequent weekly monotherapy oral methotrexate 12.5 mg for several weeks. Methotrexate was tapered and discontinued. After several weeks of no treatment, she relapsed with the same symptoms. MRI brain revealed return of the diffusely enhancing meninges. She was then retreated with a higher dose of oral weekly methotrexate 25 mg x 4 weeks which failed to induce a clinical or MRI remission.

Patient traveled to another state where methotrexate 25 mg-per week was continued and she was given rituximab 375mg/m$^2$ per standard infusion rate protocol. Within forty-

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eight hours, patient developed chest pain, nausea, dyspnea, and diaphoresis. She was diagnosed with new onset atrial fibrillation, a new left bundle branch block and unstable angina. Left heart catheterization detected 95% proximal left anterior descending artery (pLAD) occlusion. When the guidewire was passed, the patient became acutely hypoxic and then had a pulseless electrical activity arrest. An Impella CP® was inserted, and a drug eluting stent was placed in the pLAD. Patient was intubated and placed on a ventilator. For twenty-four hours and expired from cardiogenic shock.

## Discussion

This patient was 78 year old female with no prior cardiac history and no major risk factors for coronary artery disease. Forty-eight hours after rituximab was infused at a dose of 375mg/m$^2$ for off label treatment of IHPM, she develops atrial fibrillation and dies from cardiogenic shock while stenting the 95% occlusion of the pLAD.

The most common adverse reaction reported with rituximab is hypersensitivity reactions. However, other serious reactions such as hepatitis B reactivation, bowel obstruction, cardiac arrhythmias, acute coronary syndromes (ACS) or ischemia have also been documented in the literature [14]. The proposed mechanism of myocardial infarction for ACS following rituximab infusion is the release of cytokines, which cause vasoconstriction, platelet activation, and/or rupture of atherosclerotic plaque [4]. In our case, it is likely the asymptomatic LAD plaque was preexistent and vulnerable to cytokine release causing rupture or dissection of the plaque causing myocardial infarction. It is speculative that pretreating the patient with high dose steroids may have stabilized the pLAD occlusion. Recently, tocilizumab, an interleukin-6 antagonist, was granted FDA approval for the treatment of cytokine release syndrome in patients who received chimeric antigen receptor-T cell therapy. Although off label, this treatment may have been considered in this patient to stabilize plaque and prevent rupture might have stabilized the plaque thereby preventing rupture and occlusion from cytokine release allowing revascularization with stent insertion or emergency coronary bypass graft surgery to prevent myocardial infarction.

Cardiovascular toxicity in the form of cardiac dysrhythmias has been reported in 8% of patients treated with rituximab for lymphoma [3]. The "cytokine release syndrome" which includes myocardial infarction can be seen in 10% of patients treated with rituximab usually with hypotension and bronchospasm [4]. Myocardial infarctions are rare [5] but have been reported in numerous reports and reviews [6-13]. Uneasiness and sweating 5 min after rituximab infusion correlated with an electrocardiogram revealing ST elevation in inferior leads, which did not subside even after stopping the rituximab infusion. Troponin T level was elevated. Coronary angiography showed a complete thrombotic occlusion of the right coronary artery, in the absence of abnormalities in the other coronary arteries. Angioplasty was performed and the patient survived [7].

We suspect coronary occlusion from rituximab is underreported. As more rituximab is being used for off label disorders such as IgG4-RD and its localized presentation such as this case of IHPM, the incidence will only rise. Our case had no history or risk factors for coronary artery disease except for advanced age. In this case, given the localized disease and advanced age, and other treatment options such as azathioprine, mycophenolate, cyclophosphamide, repeat MTX+steroids or combination therapy with steroids could have been considered. As an increasing number of "older" patients are being referred for the expanding indications and off label uses of rituximab, it is strongly suggested that meticulous screening for ischemic heart disease be performed.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

| Authors' contributions | JAC | RR | AP |
|---|---|---|---|
| Research concept and design | ✓ | ✓ | ✓ |
| Collection and/or assembly of data | ✓ | ✓ | -- |
| Data analysis and interpretation | ✓ | ✓ | -- |
| Writing the article | ✓ | ✓ | ✓ |
| Critical revision of the article | ✓ | ✓ | ✓ |
| Final approval of article | ✓ | -- | -- |
| Statistical analysis | ✓ | ✓ | ✓ |

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