Rituximab Use and Hypogammaglobulinemia

**Patient:** Female, 59-year-old

**Final Diagnosis:** Granulomatosis with polyangiitis

**Symptoms:** Dyspnea

**Medication:** Rituximab

**Clinical Procedure:** —

**Specialty:** Rheumatology

**Objective:** Diagnostic/therapeutic accidents

**Background:** Rituximab is a genetically engineered chimeric (murine-human) monoclonal antibody (mAb) directed against CD20 antigen on the surface of B cells. Commonly reported adverse effects are chills and fevers, which are usually associated with the first infusion. Recent studies have shown an association between rituximab use and low immunoglobulin (Ig) level due to a reduction in plasma cell precursors, which leads to an increased risk of infections with the use of rituximab.

**Case Report:** We present a case of hypogammaglobulinemia associated with rituximab use in a patient with Granulomatosis with Polyangiitis (GPA). A 59-year-old woman presented with shortness of breath. After an extensive workup, she was diagnosed with GPA. She received rituximab for the induction of remission. Laboratory workup, which was done five days after she received the second rituximab dose, showed IgG and IgM levels below the level of normal. One month after her second dose of rituximab, she presented to the Medical Intensive Care Unit as a transfer from an outside facility intubated and sedated due to acute respiratory failure secondary to septic shock with *E. coli* bacteremia. The patient died on admission despite aggressive management, including the ACLS protocol.

**Conclusions:** Rituximab is an effective medication in the management of ANCA-associated vasculitis. Obtaining an immunoglobulin level at baseline and before each rituximab cycle is of great clinical importance and helps guide physicians in prescribing B cell-targeted therapy.

**MeSH Keywords:** Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis • Immunoglobulin G • Immunotherapy

**Full-text PDF:** [https://www.amjcaserep.com/abstract/index/idArt/920681](https://www.amjcaserep.com/abstract/index/idArt/920681)
Background

Granulomatosis with polyangiitis (GPA), formerly known as Wegener’s granulomatosis, is an ANCA-associated vasculitis (AAV) that usually affects small and medium vessels. It usually affects upper and lower airway tracts and the kidneys. The evolution of AAV without treatment will lead to death [1]. Treatment of AAV is based on an induction phase followed by a maintenance phase. Glucocorticoids associated with cyclophosphamide or rituximab are usually used in the induction phase. The maintenance phase is usually based on rituximab to prevent relapses [2–4].

Rituximab is a genetically engineered chimeric (murine-human) monoclonal antibody (mAb) directed against CD20 antigen on the surface of B cells. Rituximab has demonstrated efficacy in the treatment of various rheumatologic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and AAV. Commonly reported adverse effects are chills and fevers, which are usually associated with the first infusion [5]. Recent studies have shown an association between rituximab use and low immunoglobulin (Ig) level due to a reduction in plasma cell precursors, which leads to an increased risk of infections with the use of rituximab [6,7].

Case Report

A 59-year-old white woman with no significant past medical history presented as a transfer from an outside facility (OSF), complaining of shortness of breath. One month before her admission, she noticed progressively worsening exertional dyspnea, cough, and weakness in her legs. In the OSF, she was found to be in atrial fibrillation with a rapid ventricular rate. She was started on amiodarone and an anticoagulant and was found to be in atrial fibrillation with a rapid ventricular rate. She was doing fairly well at that time, with no fevers or concern for infection, and a plan was made to monitor her closely. She was receiving a dose of 1 gm of rituximab while she was being admitted and was started on ganciclovir by ID for possible CMV reactivation prophylactically, given her immunosuppression. After her first rituximab dose, she experienced nausea, chills, and rigors, which resolved on slowing the infusion, and as-needed IV hydrocortisone. Due to scheduling issues, she had received her second dose of rituximab (1 gm) one month (instead of two weeks) after the first dose, which she tolerated well. Laboratory workup, which was done five days after the second rituximab dose, showed IgG and IgM levels below the level of normal, IgG of 308 mg/dL (610–1616), and IgM 27 mg/dL (35–242). She was doing fairly well at that time, with no fevers or concern for infection, and a plan was made to monitor her closely. One month after her second dose of rituximab, she presented again to the Medical Intensive Care Unit as a transfer from an OSF, intubated and sedated due to acute respiratory failure secondary to septic shock with E. coli bacteremia. Despite aggressive management, including the ACLS protocol, the patient died on admission.

Discussion

Rituximab is an effective medication in inducing and maintaining remission in patients with AAV. Infections and hypogammaglobulinemia are not commonly reported with the use of rituximab. Low IgG levels at baseline seem to significantly contribute to hypogammaglobulinemia and serious infections associated with rituximab use [8]. A retrospective study showed that severe hypogammaglobulinemia was associated with a higher risk of infections requiring hospitalization after induction with rituximab [7]. Another study was conducted on patients with GPA, and serum Ig levels were measured prior to each rituximab infusion. Hypogammaglobulinemia occurred in one-quarter of the patients. Serum Ig levels decreased during rituximab maintenance, but the largest decrease occurred after the first infusion [9]. Rituximab usually depletes CD20+ B cells by an average of 6–12 months, with longer periods of depletion in patients with AAV [6].

Our patient did not have a history of recurrent infections (sinusitis, bronchitis, or pneumonia), organomegaly, or cytopenias; therefore, the suspicion for primary hypogammaglobulinemia was low at that time. Unfortunately, baseline immunoglobulin levels were not obtained in this patient before induction with rituximab; therefore, primary hypogammaglobulinemia was not ruled out in this patient. However, IgG and IgM levels were obtained five days after the second dose of rituximab, and both were below the normal level, which is possibly iatrogenic secondary antibody deficiency following rituximab use. This case shows the importance of obtaining an immunoglobulin
level (IgG, IgA, and IgM) at baseline and before each rituximab cycle to identify patients who are at risk for serious infections [10]. Patients may eventually require immunoglobulin replacement therapy (IGRT), as antibiotics alone are not adequate for preventing and treating infections. Currently, there are no available consensus guidelines for the use of IGRT in patients with iatrogenic secondary antibody deficiency following rituximab use. A recent systematic review highlights the induction of sustained antibody deficiency after using IGRT; therefore, consensus guidelines are needed for appropriate assessment and treatment for iatrogenic secondary antibody deficiency [11].

References:

1. Reinhold-Keller E, Beuge N, Latza U et al: An interdisciplinary approach to the care of patients with Wegener’s granulomatosis: Long-term outcome in 155 patients. Arthritis Rheum, 2000; 43(5): 1021–32
2. Timlin H, Lee SM, Manno RL et al: Rituximab for remission induction in elderly patients with ANCA associated vasculitis. Semin Arthritis Rheum, 2015; 45(1): 67–69
3. Geetha D, Specks U, Stone JH et al: Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. J Am Soc Nephrol, 2015; 26(4): 976–85
4. Stone JH, Merkel PA, Spiera R et al: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med, 2010; 363(3): 221–32
5. Leget GA, Czuczman MS: Use of rituximab, the new FDA-approved antibody. Curr Opin Oncol, 1998; 10(6): 548–51
6. Marco H, Smith RM, Jones RB et al: The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. BMC Musculoskelet Disord, 2014; 15(1): 1–9
7. Shah S, Jaggi K, Greenberg K, Geetha D: Immunoglobulin levels and infection risk with rituximab induction for anti-neutrophil cytoplasmic antibody-associated vasculitis. Clin Kidney J, 2017; 10(4): 470–74
8. Besada E: Low immunoglobulin levels increase the risk of severe hypogammaglobulinemia in granulomatosis with polyangiitis patients receiving rituximab. BMC Musculoskelet Disord, 2016; 17: 6
9. Besada E, Koldingsnes W, Nossent JC: Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. Rheumatology (Oxford), 2014; 53(10): 1818–24
10. Md Yusof MY, Vital EM, McElvenny DM et al: Predicting severe infection and effects of hypogammaglobulinemia during therapy with rituximab in rheumatic and musculoskeletal diseases. Arthritis Rheumatol, 2019; 71(11): 1812–23
11. Wijetilleka S, Mukhtyar C, Jayne D et al: Immunoglobulin replacement for secondary immunodeficiency after B-cell targeted therapies in autoimmune rheumatic disease: Systematic literature review. Autoimmun Rev, 2019; 18(5): 535–41

Conclusions

Rituximab is an effective medication in the management of AAV. Obtaining an immunoglobulin level at baseline and before each rituximab cycle is of great clinical importance and helps to guide physicians in prescribing B cell-targeted therapy. Low baseline immunoglobulin levels significantly contribute to hypogammaglobulinemia and serious infections associated with rituximab and other B cell-targeted therapy. With the huge development of immunotherapeutic agents, it is important for physicians to remain attentive and keenly observant for any adverse effects of these medications to be able to intervene promptly and improve patient outcomes.

Conflicts of Interest

None.