

# A Case Report of Rituximab Induced Angioedema

DHAIVAT SHUKLA<sup>1</sup>, KARAN SHAH<sup>2</sup>, SAPAN PANDYA<sup>3</sup>, SUPRIYA MALHOTRA<sup>4</sup>, PANKAJ PATEL<sup>5</sup>

## ABSTRACT

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. It has been approved for rheumatoid arthritis and is a promising new agent in the treatment of several autoimmune neurological disorders and also Sjögren's syndrome. Common adverse reactions to treatment with Rituximab include infusion reactions including angioedema and hypersensitivity reactions. In the present case, we observed severe angioedema after low dose of Rituximab therapy. Clinicians should be vigilant when using Rituximab for such hypersensitivity phenomenon occurring despite pre-medicating with glucocorticoids.

**Keywords:** Hypersensitivity reactions, Rheumatology, Sjögren's syndrome

## CASE REPORT

A 60-year-old female presented to the Department of Rheumatology, Sheth V.S. General Hospital, Ahmedabad, India, with the chief complaints of dry mouth, fatigue and pain in joints for a week. She was a known case Sjögren's syndrome for seven years. She was taking Tab. Hydroxychloroquine 200 mg once daily, Tab. Prednisone 5 mg once daily and Tab. Folic Acid 5 mg once daily for the same. Despite being on this treatment, her ESSDAI (EULAR Sjögren's syndrome disease activity index) score was 13 and she was not relieved of her symptoms [1]. She was admitted and infused with Rituximab 100 mg slowly intravenously over three hours. Premedication in the form of Methylprednisolone was administered before starting Rituximab infusion. She was discharged the same day. Patient returned the next day with the chief complaints of severe itchy rash all over the body. There were multiple, small, well defined, annular, non-tender, non-scaly, non-blanchable erythematous plaques with few superficial erosions over chest, abdomen and left forearm [Table/Fig-1]. This was thought to be angioedema mostly due to Rituximab. It was managed with Hydrocortisone 100 mg and Pheniramine maleate 22.75 mg/2 mL stat. Patient recovered after the same. This Adverse Drug Reaction (ADR) was reported to nearest PvPI (The Pharmacovigilance Program of India)-ADR Monitoring Centre with Report id 2017-64381. After recovery, the patient was started on Tab. Hydroxychloroquine 300 mg once daily and Tab. Prednisolone 20 mg once daily. Patient is symptomatically better since then.

## DISCUSSION

Rituximab is a genetically engineered chimeric murine/human



**[Table/Fig-1]:** Clinical picture of the patient.

monoclonal IgG1 kappa antibody directed against CD20 antigen [2]. Complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity are direct effects and structural changes, apoptosis, and sensitisation of cancer cells to chemotherapy are indirect effects of Rituximab [2]. Rituximab appears to be effective in several autoimmune disorders by causing B-cell depletion [3]. Latest treatment guidelines for Sjögren's syndrome are suggestive of label use of Rituximab as a therapeutic option in patients with primary Sjögren's syndrome for whom conventional therapies have proven insufficient [4]. This is based on category B level of evidence and class IIIb strength of recommendation. Significant number of Rituximab-associated serious adverse events affecting various systems has been reported [5]. The incidence of angioedema caused by intravenous immunoglobulin therapy is 11% [6]. Serious and sometimes fatal complications of Rituximab including grade 3 and 4 adverse reactions have also been reported in 1% of patients [7]. Angioedema is a potentially serious side effect of Rituximab therapy. The aetiology of angioedema caused by Rituximab is explained by 'cytokine release syndrome' that has been described after Rituximab infusions [8]. 'Cytokine release syndrome' is a symptom complex associated with the use of many monoclonal antibodies. It results from the release of cytokines from cells targeted by the antibody as well as immune effector cells recruited to the area. When cytokines are released into the circulation, systemic symptoms such as fever, nausea, chills, hypotension, angioedema, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea can result [9]. Previous studies suggest that the frequency of infusion reactions, which form the bulk of major ADRs due to Rituximab administration, decreased in patients who were premedicated with intravenous glucocorticoids. In contrast with the same, our patient had the ADR despite being pre medicated with glucocorticoid [10]. Usually infusion reactions occur within 24 hours of the infusion and are dose dependent [11]. In this case it happened after seven hours of infusion but the dose of Rituximab was much lesser than recommended (100 mg instead of 500 mg). In one similar incidence, a patient developed serum sickness after the first administration of Rituximab and severe angioedema after the second dose [12].

## CONCLUSION

Rituximab can cause angioedema despite premedication with glucocorticoids. So, clinicians should be vigilant towards such hypersensitivity phenomenon while using Rituximab.

## REFERENCES

- [1] Seror R, Bowman S, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, et al. EULAR Sjogren's syndrome disease activity index (ESSDAI): a user guide. *RMD Open*. 2015;1(1):000022.
- [2] Rituxan (Rituximab): Side Effects, Interactions, Warning, Dosage & Uses. Retrieved from RxList.
- [3] Kosmidis M, Dalakas M. Practical considerations on the use of rituximab in autoimmune neurological disorders. *Ther Adv Neurol Disord*. 2010;3(2):93-105.
- [4] Carsons S, Vivino F, Parke A, Carteron N, Sankar V, Brasington R, et al. Treatment guidelines for rheumatologic manifestations of sjogren's syndrome: use of biologic agents, management of fatigue, and inflammatory musculoskeletal pain. *Arthritis Care Res*. 2017;69(4):517-27.
- [5] Retrieved from *VigiAccess™* Database.
- [6] Retrieved from *Drugs@FDA*, US Food and Drug Administration.
- [7] Schwartzberg L, Stepanski E, Walker M, Mathias S, Houts A, Fortner B. Implications of IV monoclonal antibody infusion reaction for the patient, caregiver, and practice: results of a multicenter study. *Support Care Cancer*. 2008;17(1):91-98.
- [8] Jensen M, Winkler U, Mancke O, Diehl V, Engert A. Rapid tumor lysis in a patient with B-cell chronic lymphocytic leukemia and lymphocytosis treated with an anti-CD20 monoclonal antibody (IDEC-C2B8, rituximab). *Ann Hematol*. 1998;77(1-2):89-91.
- [9] Breslin S. Cytokine-release syndrome: overview and nursing implications. *Clin J Oncol Nurs*. 2007;11(0):37-41.
- [10] Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum*. 2006;54(5):1390-400.
- [11] Ghielmini M, Rufibach K, Salles G, Leoncini-Francini L, Léger-Falandry C, Cogliatti S, et al. Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK). *Ann Onco*. 2005;16(10):1675-82.
- [12] Kumar A, Khamkar K, Gopal H. Serum sickness and severe angioedema following rituximab therapy in RA. *Int J Rheum Dis*. 2011;15(1):6-7.

### PARTICULARS OF CONTRIBUTORS:

1. Fellow, Department of Rheumatology, V.S General Hospital, Ahmedabad, Gujarat, India.
2. 2<sup>nd</sup> Year Resident, Department of Pharmacology, Smt. NHL Municipal Medical College, Ellisbridge, Ahmedabad, Gujarat, India.
3. Professor and Head, Department of Rheumatology, V.S General Hospital, Ahmedabad, Gujarat, India.
4. Professor and Head, Department of Pharmacology, Smt. NHL Municipal Medical College, Ellisbridge, Ahmedabad, Gujarat, India.
5. Dean, Smt. NHL Municipal Medical College, Ellisbridge, Ahmedabad, Gujarat, India.

### NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Karan Shah,  
2<sup>nd</sup> Year Resident, Department of Pharmacology, Smt. NHL Municipal Medical College, Ellisbridge,  
Ahmedabad-380006, Gujarat, India.  
E-mail: karannhl@hotmail.com

Date of Submission: **Jan 16, 2018**  
Date of Peer Review: **Mar 31, 2018**  
Date of Acceptance: **Jun 25, 2018**  
Date of Publishing: **Sep 01, 2018**

FINANCIAL OR OTHER COMPETING INTERESTS: None.