Biomedical and Case Reports Open Access Open Journal

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Case Report

A Rare Case of Rituximab Induced Allergic Interstitial Nephritis with a Good Response to Glucocorticoids

Nalinikumari Gandhe[1], Qunfang Li[2], Vrushali Dabak[3*], Vijayalakshmi Donthireddy[4]

[1]Gandhe, Senior Staff Physician, Henry Ford Health System, Detroit MI, USA
[2]Promedica Hematology/Oncology Associates Sylvania, OH 43560, USA
[3]Associate Program Director Hematology and Oncology, Henry Ford Health System, Detroit MI, USA
[4]Program Director Hematology and Oncology, Henry Ford Health System, Detroit MI, USA

Correspondence to: Vrushali Dabak, Associate Program Director Hematology and Medical Oncology, Henry Ford Health System, Detroit MI. USA; Email address-vdabak1@hfhs.org

Received: Jul 14th, 2021; **Accepted:** Jul 19th, 2021; **Published:** Jul 19th, 2021

Citation: Gandhe N, Li Q, Dabak V, Donthireddy V. A rare case of rituximab induced allergic interstitial nephritis with a good response to glucocorticoids. Biom Case Rep Open A Open J. 2021; 2(2): 80-83. doi: 10.33169/biomcase.BACROAOJ-2-122

ABSTRACT

Rituximab is a chimeric anti-CD20 monoclonal antibody that has been widely used to treat CD 20 positive hematologic malignancies and some autoimmune conditions. Although usually well tolerated, an increasing number of serious complications related to rituximab have been noted with its wide usage. We report a 67-year-old man who developed biopsy-proven Allergic Interstitial Nephritis (AIN) after treatment with rituximab for his Primary Central Nervous System Lymphoma (PCNSL). Rituximab-induced AIN was confirmed by kidney biopsy, and his kidney function improved to his baseline with supportive care and four weeks of steroid treatment. While rare, AIN could be a possible adverse effect of rituximab. To our knowledge, this is the first case report of a biopsy-proven AIN from rituximab. The association of AIN and rituximab in our case necessitates a high index of suspicion to facilitate early detection of AIN and timely discontinuation of the offending medication.

Keywords: *Rituximab; Drug induced allergic interstitial nephritis.*

INTRODUCTION

Rituximab was the first and widely used therapeutic monoclonal antibody in clinical practice to treat CD20 positive hematological malignancies and other benign, autoimmune diseases such as rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis. Engineered as a chimeric murine/human monoclonal antibody, rituximab binds specifically to the transmembrane antigen CD20, which is present on the cell surface of pre-B lymphocytes and mature B lymphocytes. Rituximab has revolutionized the treatment of patients with B-cell malignancies. It is currently part of the standard of care for CD20 positive B-cell non-Hodgkin lymphomas (NHLs), chronic lymphocytic leukemia (CLL), and mantle cell lymphoma.[1]

Common adverse events secondary to rituximab are infusion reactions, infections, cytopenia, hepatitis B virus reactivation, progressive multifocal leukoencephalopathy, and cardiovascular events, most commonly hypotension, arrhythmias, and angina pectoris. Acute Tumor Lysis Syndrome (ATLS) leading to acute kidney injury has been observed after rituximab monotherapy, especially in conditions with a high tumor burden, like NHL.[2] Urine output and trends in serum creatinine need to be closely monitored in patients receiving rituximab. However, the rare and potentially life-threatening complication of Allergic Interstitial Nephritis (AIN) is not well known or documented in the medical literature. Here we report a rare case of rituximab-induced AIN in a patient diagnosed with primary central nervous system lymphoma (PCNSL). The patient's kidney failure resolved after permanent rituximab discontinuation, and he responded very well to prednisone treatment. The association of AIN and rituximab described in our case highlights the importance of increased awareness and early recognition of this severe complication, which will lead to prompt management of AIN and better patient outcomes.

CASE PRESENTATION

A 69-year-old male with a past medical history of hypertension, hyperlipidemia, and coronary artery disease status post stent placement presented with right-side weakness and unstable gait of 2 months duration.

He denied any headache, vision changes, or altered mental status. The patient's medication list was reviewed Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Proton Pump Inhibitors (PPI), or antibiotics were not part of his medication list

Magnetic Resonance Imaging (MRI) brain showed left frontal brain mass. Excisional biopsy of the lesion showed morphologic features consistent with non-germinal center Diffuse Large B-Cell Lymphoma (DLBCL), CD20 was expressed. The high proliferation fraction (MIB1 > 90%) and Bcl2 /c-MYC double expression indicated the aggressive nature of his high-grade B cell NHL. Further imaging with whole-body Positron Emission Tomography (PET) scan and MRI spine did not reveal any other lesions in his chest, abdomen, or pelvis; an ophthalmologic exam with the slit lamp ruled out any vitreoretinal involvement.

In addition, he did not have any abnormality on testicular ultrasound. Diagnosis of primary CNS lymphoma (PCNSL) was confirmed by imaging and biopsy.

The patient was started on systemic high dose methotrexate based on the Cancer and leukemia group B (CALGB) 50202 regimen, considering his overall fair performance status and normal liver, kidney functions. During his first rituximab infusion, the patient experienced infusion reaction with flushing, tachycardia, and mildly low blood pressure with SBP in the 90s, despite premedication with Benadryl and acetaminophen. Rituximab infusion was immediately stopped; the patient was given hydrocortisone 100mg, Benadryl 50mg, and Pepcid 40mg through IV, as well as one liter of normal saline. His symptoms resolved, and his blood pressure was back to his baseline. He was observed for several hours before he was discharged. Two days later, the patient was admitted for the first cycle of methotrexate at 6g/m2.

Leucovorin was given as a rescue after the high dose of methotrexate. He was given sodium bicarbonate to alkalize his urine with close monitoring of his urine PH and plasma methotrexate level. The patient was able to clear methotrexate from his bloodstream within five days. (Table 1).

Table 1. The patient's able to clear methotrexate from his bloodstream within five days

	Units	24 hours	48 hours	Day 3	Day 4	Day 5
Methotrexate level	umol/L	3.57	0.58	0.31	0.22	0.08

The patient was rechallenged with rituximab 2 days after he finished methotrexate and 4 days after his first dose of rituximab. Hydrocortisone 100 mg IV push was added as premedication before rechallenge, and the patient tolerated rituximab well with no infusion reaction at this time.

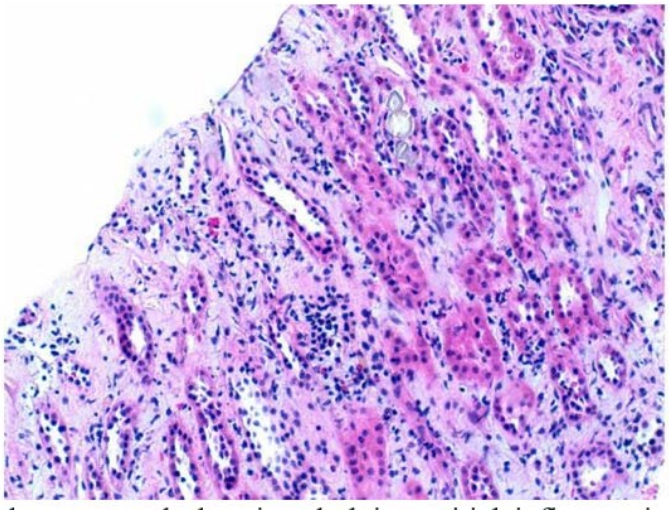
Even though his methotrexate level continued to trend down with good clearance, his creatinine increased unexpectedly from the second day after he finished rituximab. By day six, after rituximab infusion, the patient went into Acute Kidney Injury (AKI) with his creatinine at 6.11 mg/dl (reference range <1.28 mg/dl). Urinalysis showed microscopic hematuria, urine red blood cell count was 6/HPF (reference range <3/HPF). Complete blood count with differential (CBCD) showed mild anemia, hemoglobin was 10 g/dl (reference range 13.5-17.0g/dl), lymphopenia. Absolute lymphocyte count was 0.70 K/ul; he had no eosinophilia. The patient did not meet the criteria for tumor lysis syndrome.

Table 2. Serum biochemical values.

	Ref Range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day10
Serum creatinine	<1.13 mg/dl	0.94	2.01	3.38	4.79	5.69	6.11	3.84
Serum uric acid	2.5-7.5 mg/dl	6.6	6.8	6.9	7.4	7.8	7.9	6.6
Serum phosphorus	2.5-4.5 mg/dl	3.4	3.8	4.1	5.2	5.2	5.2	4
Serum calcium	8.2-10.2 mg/dl	8.2	8.1	8.6	8.7	9.2	9.3	9.1
Serum potassium	3.5-5.0 mmol/L	3.2	3.4	3.5	3.9	4.2	4.4	4.1

Renal ultrasound showed a normal appearance of the kidneys without hydronephrosis. Computerized Tomography (CT) guided kidney biopsy was performed to get a definitive diagnosis and etiology of his AKI. Biopsy demonstrated chronic tubulointerstitial inflammation with increased eosinophils, consistent with acute tubular injury with crystalline and hyaline casts, correlated with mild interstitial fibrosis. (Figure1).

Figure 1: Biopsy demonstrated chronic tubulointerstitial inflammation with increased eosinophils, consistent with acute tubular injury with crystalline and hyaline casts, correlated with mild interstitial fibrosis.



The pathology report confirmed the diagnosis of Drug-induced Allergic Interstitial Nephritis and Acute Tubular Injury. With an inconsistent timeline between methotrexate clearance and the progressive creatinine elevation, methotrexate was unlikely to be the source of his AKI. The patient's medication list was reviewed for the potential cause of AIN, and he had no recent use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), antibiotics, or any other medication with the

potential to cause AIN. Although no cases have been reported linking rituximab and AIN, the suspicion that it was the cause was high, mainly due to his prior allergic reaction to the first dose of rituximab.

The patient was started on daily prednisone 60 mg. His creatinine improved in 4 days to 3.84 mg/dl, and he was discharged home with steroid taper over 30 days. His creatinine normalized by four weeks from his first dose of prednisone. The patient did not need dialysis. Since then, rituximab was removed permanently from his treatment regimen. He was started back on systemic high dose methotrexate with Leucovorin rescue. His Methotrexate dose was slowly titrated up to 8g/m2 by cycle 5; he achieved methotrexate clearance within five days with no significant side effects. His kidney function had been stable after steroid taper with peak creatine at 1.69 mg/dl during cycle two and cycle three of systemic chemotherapy.

DISCUSSION

Drug-Induced Allergic Interstitial Nephritis (DIAIN) is the most common form of AIN. Although any drug can potentially cause drug-induced AIN, antibiotics, non-steroidal anti-inflammatory drugs, and proton pump inhibitors are the most frequent offenders.[3-7]

DIAIN has a variable clinical presentation and often presents without the hallmark features of eosinophilia, rash, and fever.[4,6,7] Drug-induced AIN occurs days to weeks after exposure.[6] Our patient developed Acute Kidney Injury (AKI) within a few days after rituximab infusion, and he did not have the classic presentation of AIN. Timeline from drug intake to onset of disease is variable.[4] AIN can also be slowly progressive, resulting in a delayed patient presentation with acute kidney injury.

In most cases, the etiology is a delayed hypersensitivity immune reaction driven by antigen-reactive T cells; therefore, the reaction is idiosyncratic, not dose-related, and occurs with drug rechallenge.[7] The frequency of allergic interstitial nephritis is likely underestimated, as the diagnosis can only be definitively confirmed with kidney biopsy evaluation. [4,7-9] Additionally, older adults subject to polypharmacy are more likely to develop AIN but may not be considered good candidates for invasive procedures such as a renal biopsy.[7] When evaluating renal biopsies performed for acute kidney injury, interstitial nephritis was noted in 5% to 27%% of cases.[7]

Rituximab is a monoclonal antibody that induces apoptosis in human B cell lymphoma cells. Acute infusion reactions consisting of fever, chills, rigors, rash, and occasionally bronchospasm and hypotension are the most common adverse effects. This effect is known as a 'cytokine-release syndrome' and is thought to be due to robust cytokine release.[10] Our patient experienced infusion reaction with flushing, tachycardia, and mildly low blood pressure during his first infusion. Rituxan has not been correlated with allergic interstitial nephritis in any case reports. Here, we report the first case of Rituxan- induced AIN, which was verified by a kidney biopsy. Our patient's prior allergic infusion reaction gave us the first hint and pointed to rituximab as the AIN-causing agent. Moreover, this was supported by the stable baseline creatinine after discontinued rituximab. The patient was continued on a higher dose of Methotrexate after he recovered from AIN.

The essential step is discontinuing the offending agent in patients with suspected or confirmed allergic interstitial nephritis.[4,7,11,12] Immunosuppressive therapy has been used to treat AINs, but the paucity of randomized controlled trials has limited the evidence for this approach.[4]

Recent studies strongly suggest that early steroid administration (within seven days after diagnosis) improves the recovery of renal function, decreasing the risk of chronic renal impairment and End-Stage Renal Disease (ESRD).[3] The addition of steroids to our patient's treatment led to a complete resolution of his kidney failure. Steroids are generally considered after diagnosis of AIN to avoid subsequent interstitial fibrosis and incomplete recovery of renal function.

Steroids should be started promptly if there has been no improvement in renal function within three to seven days after withdrawal of the offending drug.[3,13,14]

There have been small case series evaluating mycophenolate mofetil and cyclosporine as therapy options in glucocorticoid-dependent and refractory patients.[4]

CONCLUSION

Allergic Interstitial Nephritis (AIN) should be considered as a differential diagnosis and a reversible cause of acute kidney injury in patients with worsening renal function with new medication exposure. Given the increasing use of rituximab, it is essential to recognize that rituximab can cause Drug-induced AIN and acute kidney injury.

The mainstay of treatment in AIN is the early identification and removal of the offending agent. Steroid therapy should also consider during the first week of diagnosis in addition to supportive care.

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CONFLICTS OF INTEREST

None.

REFERENCES

1. Salles G, Barrett M, Foà R, et al. Rituximab in B-Cell Hematologic Malignancies: A Review of 20 Years of Clinical Experience. *Adv Ther*. 2017; 34(10): 2232-2273. doi: 10.1007/s12325-017-0612-x

2. Kasi PM, Tawbi HA, Oddis CV, Kulkarni HS. Clinical Review: Serious Adverse Events Associated with The Use of Rituximab - A Critical Care Perspective. *Crit Care*. 2012; 16(4): 231. doi: 10.1186/cc11304

3. Praga M, González E. Acute Interstitial Nephritis. *Kidney Int*. 2010; 77(11): 956-961. doi: 10.1038/ki.2010.89

4. Moledina DG, Perazella MA. Drug-Induced Acute Interstitial Nephritis. *Clin J Am Soc Nephrol*. 2017; 12(12): 2046-2049. doi: 10.2215/CJN.07630717

5. Chowdry AM, Azad H, Mir I, et al. Drug-Induced Acute Interstitial Nephritis: Prospective Randomized Trial Comparing Oral Steroids and

High-Dose Intravenous Pulse Steroid Therapy in Guiding The Treatment of this Condition. *Saudi J Kidney Dis Transpl*. 2018; 29(3): 598-607. doi: 10.4103/1319-2442.235171

6. Muriithi AK, Leung N, Valeri AM, Cornell LD, Sethi S, Fidler ME, et al. Biopsy-Proven Acute Interstitial Nephritis, 1993-2011: A Case Series. *Am J Kidney Dis*. 2014; 64(4): 558-566. doi: 10.1053/j.ajkd.2014.04.027

7. Nast CC. Medication-Induced Interstitial Nephritis in the 21st Century. *Adv Chronic Kidney Dis*. 2017; 24(2): 72-79. doi: 10.1053/j.ackd.2016.11.016

8. Perazella MA. Diagnosing Drug-Induced AIN in The Hospitalized Patient: A Challenge for The Clinician. *Clin Nephrol*. 2014; 81(6): 381-388. doi: 10.5414/CN108301

9. Perazella MA, Markowitz GS. Drug-induced Acute Interstitial Nephritis. *Nat Rev Nephrol*. 2010; 6(8): 461-470. doi: 10.1038/nrneph.2010.71

10. Vogel WH. Infusion Reactions: Diagnosis, Assessment, and Management. *Clin J Oncol Nurs*. 2010; 14(2): E10-21. doi: 10.1188/10.CJON.E10-E21

11. Galesić K, Prkacin I, Tisljar M, Horvatić I, Ljubanović DG. Drug Induced Allergic Interstitial Nephritis. *Lijec Vjesn*. 2011; 133(7-8): 276-283.

12. González E, Gutiérrez E, Galeano C, Chevia C, de Sequera P, Bernis C, et al. Early Steroid Treatment Improves The Recovery of Renal Function in Patients With Drug-Induced Acute Interstitial Nephritis. *Kidney Int*. 2008; 73(8): 940-946. doi: 10.1038/sj.ki.5002776

13. Golbin L, Dolley-Hitze T, Lorcy N, Rioux-Leclercq N, Vigneau C. Drug-Induced Acute Interstitial Nephritis with Nifedipine. *Case Rep Nephrol*. 2016; 2016: 1971465. doi: 10.1155/2016/1971465

14. Ramachandran R, Kumar K, Nada R, Jha V, Gupta KL, Kohli HS. Drug-Induced Acute Interstitial Nephritis: A Clinicopathological Study and Comparative Trial Of Steroid Regimens. *Indian J Nephrol*. 2015; 25(5): 281-286. doi: 10.4103/0971-4065.147766