Journal of Biosciences and Medicines, 2024, 12, 89-94
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Rituximab Induced Vasculitis: Dose the Antigen-Antibody Complex of Rituximab Play a Role in Developing Leukocytoclastic Vasculitis?

—A Case Report and Review of the Literature

Ahmed A. AlTaroti[1*], Zahra Z. AlZahir[1], Salah Abohelaika[2]

[1]Department of Internal Medicine, Qatif Central Hospital, Qatif, Saudi Arabia
[2]Research Centre, Qatif Central Hospital, Qatif, Saudi Arabia
Email: *ahmedtaruti@yahoo.com

How to cite this paper: AlTaroti, A.A., Al-Zahir, Z.Z. and Abohelaika, S. (2024) Rituximab Induced Vasculitis: Dose the Antigen-Antibody Complex of Rituximab Play a Role in Developing Leukocytoclastic Vasculitis? *Journal of Biosciences and Medicines*, **12**, 89-94.
https://doi.org/10.4236/jbm.2024.129010

Received: August 5, 2024
Accepted: September 8, 2024
Published: September 11, 2024

Abstract

Rituximab is a monoclonal antibody that targets CD20, which is a specific B-cell surface antigen. It was the first monoclonal antibody that was approved for the treatment of non-Hodgkin lymphoma, rheumatoid arthritis, and other cutaneous lymphoid malignancies. There are many off-label uses of rituximab, such as systemic lupus erythematosus, autoimmune hemolytic anemia, multiple sclerosis, graft-versus-host disease, chronic lymphocytic leukemia, and chronic immune-mediated thrombocytopenia. Among the rare side effects associated with rituximab treatment is vasculitis, more specifically, leukocytoclastic vasculitis. Here, we describe a 21-year-old Saudi female with leukocytoclastic vasculitis occurring three months after treatment with rituximab.

Keywords

Rheumatoid Arthritis, Rituximab, Vasculitis, Leukocytoclastic Vasculitis

1. Introduction

Rituximab is a monoclonal antibody that targets CD20, which is a specific B-cell surface antigen. It was the first monoclonal antibody approved for the treatment of non-Hodgkin lymphoma, rheumatoid arthritis, and other cutaneous lymphoid malignancies [1] [2]. There are many off-label uses of rituximab, such as systemic lupus erythematosus, autoimmune hemolytic anemia, multiple sclerosis, graft-versus-host disease, chronic lymphocytic leukemia, and chronic immune-mediated

thrombocytopenia [1]. Rituximab's main side effects include headache, fever, dyspnea, nausea and hypotension, which are particularly due to antibody-antigen interactions [3]. Cutaneous side effects after administration of rituximab can occur, including Stevens-Johnson Syndrome, pro-inflammatory syndrome that mimics acute rheumatoid arthritis, Merkel cell carcinoma, and vasculitis [2] [3]. Rituximab-induced vasculitis is reported in four published case reports [2]-[5]. Here, we describe a case of a young woman with rheumatoid arthritis who developed leukocytoclastic vasculitis after receiving two doses of rituximab.

2. Case

A 21-year-old Saudi female with a history of sero-positive rheumatoid arthritis. The patient was diagnosed in 2004 based on clinical presentation of symmetrical polyarthritis involving Proximal Interphalangeal (PIP), wrist, Metatarsophalangeal (MTP) and knee joints, with positive Rheumatoid Factor (RF) & Cyclic Citrullinated Peptide Antibody (Anti-CCP) with polyarthopathy and positive rheumatoid serology. The patient also had hypothyroidism, knee osteoarthritis, and status post-bariatric surgery. She was refractory to treatment with steroid (prednisolone 5 - 10 mg daily orally for 6 years), methotrexate (15 mg orally once weekly for 2 years), chloroquine (250 mg/day daily orally for 6 years), infliximab (3 mg/kg intravenously at 0, 2, and 6 weeks/she received 3 doses), adalimumab (40 mg subcutaneous every two weeks/she received total 14 doses) for Rheumatoid Arthritis.

The patient was resistant to all these medications and her disease course activity showing a 28-joint Disease Activity Score (DAS 28-ESR) [6] of 4.7 despite these medications. Therefore, she was considered for treatment of rituximab (1000 mg intravenous infusion), and showed a good response to the treatment initially. After two weeks, she received rituximab second dose. However, within 24 hours after the second injection, she presented to the Emergency Department with multiple symmetrically distributed inflammatory skin lesions. Initially, skin lesions were erythematous patches, then it changed to purpuric. The skin lesions were painful, but no itchiness. The skin lesions were noted on feet, both arms and spread to the chest and face. The patient also complained of chilis, subjective fever, lower leg pain, and fatigue. She had not recently started on any other new medications. She had no recent history of travel and no contact with sick patients. Systemic clinical review was unremarkable.

Her examination revealed a conscious, alert, and oriented patient. Her vital signs were: temperature: 37.0˚C, pulse rate: 76 beat/min, O_2 saturation: 100% (at room air), blood pressure: 113/60 mmHg. Physical examination revealed diffuse palpable erythematous papules and plaques on the lower extremities, both arms and spread to the chest and face (**Figure 1**), which gives a clinical impression of vasculitis. There was no evidence of synovitis. Head and neck, pulmonary, and cardiac examinations were unremarkable, and her abdomen was soft, not tender, or distended with normal bowel sounds.

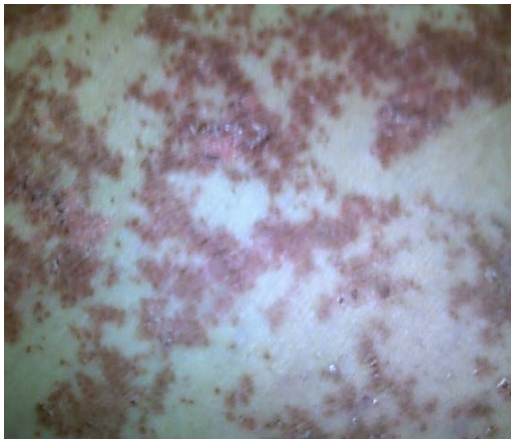

Figure 1. Diffuse palpable erythematous purpura on the lower extremities.

The laboratory tests showed a red blood cell count of 4.92×10^{12}/L, hematocrit 32.3% (49 - 54)%, hemoglobin 10.1 g/dL (13 - 17) gm/dL, white cell count 7.28×10^{9}/L (4 - 10) $\times 10^{3}$/uL, platelets 259×10^{9}/L (150 - 340) $\times 10^{3}$/uL, erythrocyte sedimentation rate 9 mm/h, C-reactive protein negative 0.3 mg/dL (normal, max 0.8), C3 74 mg/dL (normal, 80 - 152), C4 18.4 mg/dL (normal, 14 - 40). Anti-CCP (anti-Cyclic Citrullinated Peptide) positive (771.6), RF (rheumatoid factor) positive (64) (normal max 20).

The creatine phosphokinase level was 50 U/L (24 - 195 U/L). Results of renal function tests, including urinalysis and hepatic panel, were normal with the exception of an albumin level of 2.2 g/dL (3.9 - 5.2 g/dL). Results of coagulation profile were normal.

The presence of autoantibodies including cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) and perinuclear (p-)ANCA, Anti-Ro/SSA antibodies, Anti-La/SSB antibodies, Anti-DNA antibodies, Beta 2 glycoprotein antibodies, Anti-RNP (Riboncleoprotein) were all negative.

A skin biopsy showed a fragmented numerous neutrophilis with leukocytoclasis and fibrinoid necrosis of small vessel wall, which was consistent with the diagnosis of leukocytoclastic vasculitis.

Based on the clinical and histopathological findings, it was determined that the most likely cause of vasculitis in our case was either an adverse reaction to rituximab or disease activity related to rheumatoid arthritis.

The patient was treated with methylprednisolone injection (125 mg) with tapering doses, diphenhydramine, and ranitidine. The pain and rash resolved rapidly over the next 7 - 10 days of treatment.

3. Discussion

Leukocytoclastic vasculitis, also known as "hypersensitivity vasculitis", is a histopathological diagnosis of small vessel vasculitis that involves dermal post-capillary venules and internal organs [7] [8]. The pathogenesis of leukocytoclastic vasculitis

is deposition of immune complex in the small vessels and activation of the complement system. Rituximab induces cytokine release syndrome, which primarily involves tumor necrosis factor and interleukins IL-1, IL-6, and IL-8 [2] [9]. The inflammatory infiltrate is composed of neutrophils with fibrinoid necrosis and breakdown of nuclei into fragments [8].

Vasculitis most commonly is idiopathic, however, some cases are related to infection, malignancy, drug-induced, connective tissue diseases, inflammatory bowel disease, Behcet's disease, cryoglobulinemic vasculitis, IgA vasculitis, hypocomplementemic urticarial vasculitis, and rheumatoid arthritis [7] [8]. The main clinical feature of leukocytoclastic vasculitis is palpable purpura that involves the lower extremities [7].

Drug-induced vasculitis is usually after 1 - 3 weeks of drug administration [7]. However, the interval between the first administration of rituximab and the development of vasculitis is different according to the reported cases of rituximab-induced vasculitis [2] [10].

When the leukocytoclastic vasculitis is suspected, an extensive workup is needed, which includes detailed history, physical examination, and lab investigations. A platelet count, renal function test and urinalysis, serological tests for hepatitis B and C viruses, autoantibodies (anti-nuclear antibodies and anti-neutrophil cytoplasmic antibodies), complement fractions and IgA staining in biopsy specimens are all parts of the usual workout of leukocytoclastic vasculitis [8].

In our case, the patient did not show any signs of infection, or any internal organ involvement. Based on the laboratory studies and autoantibody profile, which were all negative, autoimmune diseases and ANCA-associated vasculitis were excluded. An acute infusion reaction was also one of the differential diagnoses. However, our patient did not show symptoms of infusion-related reaction, such as headache, flushing, arthralgia, fatigue or any signs of allergy. Furthermore, rheumatoid vasculitis was one of our considerations, however, our patient showed low titers of rheumatoid factor. Rheumatoid vasculitis usually involves large vessels, and typically presents with peripheral neuropathy, digital gangrene, and nail fold infarction [2]. The skin biopsy of our patient showed small vessel vasculitis without cutaneous nodules or ulcers. Therefore, the low titer of RF, small vessel vasculitis in the skin biopsy, and absence of peripheral neuropathy make the diagnosis of rheumatoid vasculitis unlikely in our patient. Considering the recent history of administration of rituximab and the other causes of vasculitis were excluded, the diagnosis was made as a case of rituximab-induced vasculitis in our case. Rituximab was stopped and the patient was treated with methylprednisolone (125 mg) with tapering doses, diphenhydramine, and ranitidine. The pain and rash resolved rapidly over the next 7 - 10 days of treatment.

When a medication is the cause of leukocytoclastic vasculitis, the prognosis is promising, and the discontinuation of drug is usually resolutive [8]. However, when a systemic vasculitis is the cause of leukocytoclastic vasculitis, higher doses of steroids or immunosuppressive agents are required according to the severity of organ involvement [8].

Table 1. Review of the cases of rituximab-induced vasculitis.

Case	Age/Sex	Diagnosis	Onset	Rituximab Dose	Treatment/Outcome	Symptoms resolved within	Reference
1	44 male	B-cell Chronic Lymphoid Leukemia	2 days after first dose	700 mg	Discontinuation of rituximab	Not mentioned	[3]
2	67 female	Follicular non-Hodgkin lymphoma	After third dose	Not mentioned	Intravenous dexamethasone and discontinuation of rituximab	7 days	[4]
3	38 male	Rheumatoid Arthritis	One day after first dose	1000 mg	Discontinuation of rituximab	14 days	[2]
4	63 male	Follicular lymphoma	After 10^{th} dose After 12^{th} dose	Not mentioned	Oral prednisolone and discontinuation of rituximab	28 days	[5]
Our case	24 female	Rheumatoid Arthritis	One day after second dose	1000 mg	Intravenous methylprednisolone and discontinuation of rituximab	10 days	

Up to our knowledge, our case appears to be the fifth case report about biopsy-proven rituximab-induced leukocytoclastic vasculitis. Table 1 presents a review of cases involving rituximab-induced vasculitis.

There is no doubt that an increasing number of cutaneous side effects of rituximab will be reported in the future. Thus, further studies are needed to determine the pathophysiology, treatment outcome, and risk factors for the vasculitis associated with rituximab treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Selewski, D.T., Shah, G.V., Mody, R.J., Rajdev, P.A. and Mukherji, S.K. (2010) Rituximab (Rituxan). *American Journal of Neuroradiology*, **31**, 1178-1180. https://doi.org/10.3174/ajnr.a2142

[2] Kim, M.J., Kim, H.O., Kim, H.Y. and Park, Y.M. (2009) Rituximab-Induced Vasculitis: A Case Report and Review of the Medical Published Work. *The Journal of Dermatology*, **36**, 284-287. https://doi.org/10.1111/j.1346-8138.2009.00639.x

[3] Dereure, O., Navarro, R., Rossi, J. and Guilhou, J. (2001) Rituximab-Induced Vasculitis. *Dermatology*, **203**, 83-84. https://doi.org/10.1159/000051713

[4] Kandula, P. and Kouides, P.A. (2006) Rituximab-induced Leukocytoclastic Vasculitis: A Case Report. *Archives of Dermatology*, **142**, 246-247. https://doi.org/10.1001/archderm.142.2.246

[5] Abe, K., Itoh, M. and Asahina, A. (2019) Rituximab-Induced Vasculitis: Does the Immune Complex of Rituximab Play a Key Role in Developing Paradoxical Adverse Events? *The Journal of Dermatology*, **46**, e311-e312. https://doi.org/10.1111/1346-8138.14872

[6] Prevoo, M.L.L., Van'T Hof, M.A., Kuper, H.H., Van Leeuwen, M.A., Van De Putte, L.B.A. and Van Riel, P.L.C.M. (1995) Modified Disease Activity Scores That Include Twenty-Eight-Joint Counts Development and Validation in a Prospective Longitudinal Study of Patients with Rheumatoid Arthritis. *Arthritis & Rheumatism*, **38**, 44-48. https://doi.org/10.1002/art.1780380107

[7] Baigrie, D. and Crane, J.S. (2020) Leukocytoclastic Vasculitis (Hypersensitivity Vasculitis). StatPearls.

[8] Fraticelli, P., Benfaremo, D. and Gabrielli, A. (2021) Diagnosis and Management of Leukocytoclastic Vasculitis. *Internal and Emergency Medicine*, **16**, 831-841.

[9] McIlwain, L., Carter, J.D., Bin-Sagheer, S., Vasey, F.B. and Nord, J. (2003) Hypersensitivity Vasculitis with Leukocytoclastic Vasculitis Secondary to Infliximab. *Journal of Clinical Gastroenterology*, **36**, 411-413. https://doi.org/10.1097/00004836-200305000-00010

[10] Hellerstedt, B. and Ahmed, A. (2003) Delayed-Type Hypersensitivity Reaction or Serum Sickness after Rituximab Treatment. *Annals of Oncology*, **14**, 1792. https://doi.org/10.1093/annonc/mdg488