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Rituximab-Induced Vasculitis: A Case Report and Literature Review

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Abstract

Introduction

Rituximab is an anti-CD20 chimeric human-murine monoclonal antibody that is effective in the treatment of some autoimmune diseases. Cutaneous vasculitis is an unusual side effect of rituximab, with only a few reported cases worldwide.

Case presentation

A 51-year-old male presented with constitutional symptoms and symmetrical palpable erythematous lesions mainly on the lower extremities after one month of using rituximab. This scenario was very impressive because of the scarcity of this type of drug side effect. However, full investigations including histopathology were done, and after the exclusion of all other causes, a diagnosis of cutaneous vasculitis was made. Fortunately, the symptoms were relieved after drug discontinuation.

Conclusion

Cutaneous vasculitis is rare but a real side effect of rituximab, which usually subsides after stopping the drug.

Keywords: Case report; Vasculitis; Rituximab; Anti-CD20; Inflammatory lesions.

Introduction

Vasculitides are a diverse group of diseases characterized by inflammation of the blood vessel walls, which are classified as large, medium, or small-vessel vasculitis depending on the size of the blood vessels affected.

One subtype of small-vessel vasculitis is cutaneous vasculitis, which is known to be a non-ANCA-associated vasculitis that exclusively affects the skin by immune complex deposition without affecting any other organs.

The incidence of cutaneous vasculitis ranges from 15 to 38 cases per million per year, with approximately 50% of cases being idiopathic **[1,2]**. However, potential causes for this condition have also been reported, such as autoimmune diseases (systemic lupus erythematous), infections (HIV, hepatitis C), and the use of certain medications.

While systemic vasculitides are one of the rarest disorders that can emerge as a drug reaction, medication reactions have been found to cause up to 30% of cutaneous small vessel vasculitis. Common medications that have been associated with this condition include penicillins, cephalosporins, minocycline, quinolones, and TNF inhibitors. Less common medications that have been associated with cutaneous vasculitis include ACE inhibitors, beta-blockers, and clindamycin. One of the rarest reported medications that have caused cutaneous vasculitis is Rituximab **[3]**.

Rituximab is a chimeric human/murine anti-CD20 monoclonal antibody that is expressed on the surface of either cancerous or normal B lymphocytes. It is currently approved for the treatment of low-grade B-cell non-Hodgkin’s lymphoma, idiopathic thrombocytopenic purpura, and rheumatoid arthritis as a single or combination therapy.

Antigen-antibody interactions can cause widespread adverse effects on a variety of body systems, such as dyspnea, chest tightness, coughing, and fever. However, more severe reactions and rare side effects, such as cutaneous small vessel vasculitis, have also been reported **[4]**.

Cutaneous small vessel vasculitis is characterized by a symmetric, non-blanchable, palpable purpura that is typically pruritic and painful, annular in shape, and primarily located in the lower extremities. A histopathological skin biopsy is required for diagnosis, which usually reveals perivascular neutrophilic infiltration with a fibrinoid breakdown of the vascular wall, also known as leukocytoclastic vasculitis **[2]**. Depending on the severity of the disease, management typically begins with the withdrawal of the causative substance or by treating the underlying cause. Immunosuppressive therapy may also be recommended.

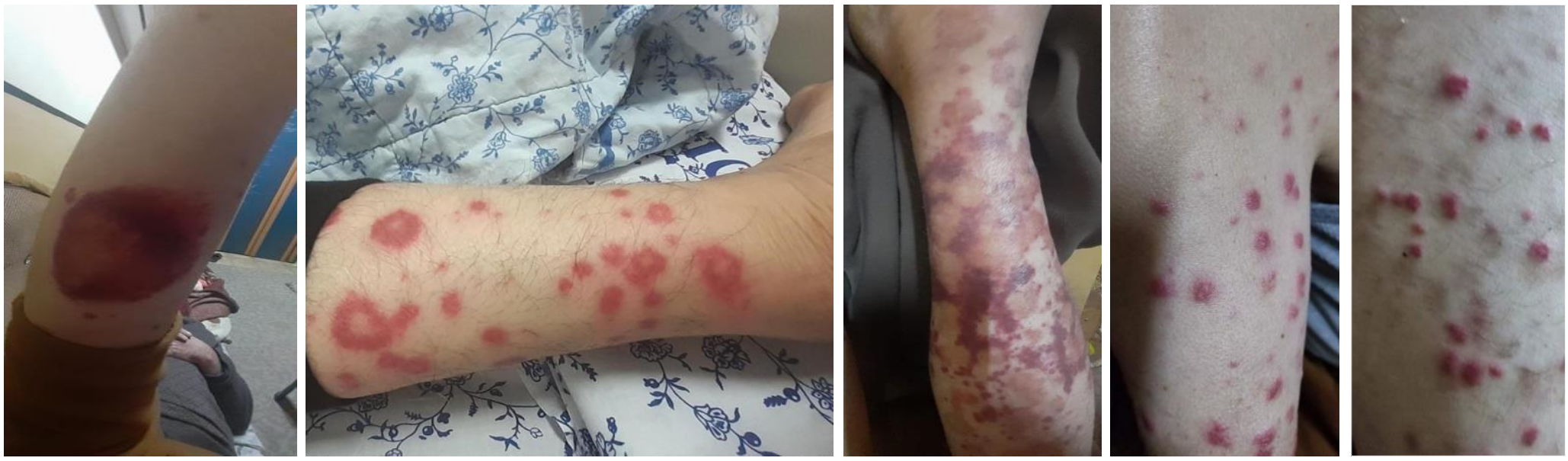
In this case report, we present a case of rituximab-induced cutaneous small vessel vasculitis in a 51-year-old male patient who was treated for low-grade B-cell non-Hodgkin's lymphoma with a combination of chemotherapy and rituximab for one-month duration.

Case Presentation

A 51-year-old male patient, known to be pre-diabetic who had a left-sided DVT event, presented complaining of neck swelling, dysphagia, anorexia, bedwetting, and fever for more than one month. After complete work-up and investigations, he was diagnosed with B-cell non-Hodgkin lymphoma on the 8th of March, 2021. After that, the patient started chemotherapy sessions which were followed by a remission two months later. After one month, rituximab infusion was added to the therapeutic regimen by his hematologist.

Following one month of treatment with Rituximab, the patient presented with lower extremities inflammatory skin rash. The lesions were symmetrically distributed on the lower limbs, particularly on the legs and ankles. The lesions then started to appear on the upper limbs bilaterally, progressing to involve the head, face, and abdomen as well. They were pruritic petechial non-blanching rounded macules, which were erythematous with a central pallor **[Figure 1]**.

Figure:1. Non-blanching petechial skin lesions after 1 month of Rituximab infusion.



The rash was associated with mild fever and fatigue, but no history of trauma. Clinical examination was otherwise unremarkable.

Laboratory tests were performed and included complete blood count (CBC), serum electrolytes, lipid profile, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Rheumatoid factor (RF), Liver function tests, kidney function tests, complement C3, complement C4, Lactate dehydrogenase (LDH), Anti-Neutrophil Cytoplasmic Antibodies-P (p-ANCA), Anti-Neutrophil Cytoplasmic Antibodies-C (c-ANCA), Anti-Nuclear Antibodies (ANA), Anti-DNA Antibodies, Hepatitis B serology, Hepatitis C antibodies, and Urine analysis. Abnormal results are shown in **[Table 1]**

Table: 1. Laboratory tests that were done for the patient with abnormal results and normal ranges.

Date	Laboratory Test	Result	Normal Ranges
17-2-2022	CRP	Positive	
	ESR	67 mm/hr	0-15(mm/hr)
03-3-2022	CBC	White blood cells (WBCs) Count = 1.54 × 10^3 /µL	3.60-10.60(x10^3/ µL)
		Absolute Neutrophil Count: 0.804 x 10^3 /µL	2-7 (x10^3/µL)
		Absolute Lymphocyte Count: 0.511 x 10^3 /µL	1-3.50(x10^3/µL)
		Absolute Eosinophil Count: 0.005 x 10^3 /µL	0.02-0.50(x10^3/µL)
		Red blood cells (RBCs) Count: 2.89 × 10^6 /µL	4.70-6.10(×10^6 /µL)
		Hematocrit= 27.6%	40-54 (%)
		Hemoglobin= 8.25 g/dl	13.50-18 (g/dl)
		Mean Corpuscular Hemoglobin Concentration (MCHC) = 29.9 g/dl	32-36 (g/dl)
		Red blood cell Distribution Width (RDW) = 15.6%	11.50-14.50 (%)
	Alkaline Phosphatase (ALP)	194 u/L	40-129 (u/L)
	C4	53 mg/dl	10-40 (mg/dl)
	LDH	121 u/L	135-225 (u/L)
	Urine analysis	Trace the amount of bacteria. Heavy urine mucus. Few urine epithelial cells. Urine RBCs/ HPF = 9-11 Urine pus cells/HPF= 20-24 Urine analysis stick blood =+1	
	Serum Creatinine (Cr)	0.67 mg/dl	0.70-1.20(mg/dl)
16-3-2022	CRP	24 mg/L	Less than 6(mg/L)
	ESR	13 mm/hr	5-15(mm/hr)

Multiple diagnostic imaging modalities were done, including computed tomography (CT) scans of the chest, neck, abdomen, and pelvis. A positron emission tomography (PET) scan of the brain was also done. Abnormal results are shown in **[Table 2]**.

Skin excisional biopsy from the lesions was done. Results revealed the presence of perivascular subcutaneous inflammatory cell infiltrates, with marked RBCs extravasation suggestive of vasculitis. No evidence of malignancy.

Table: 2. Imaging modalities that were done for the patient with abnormal findings.

Date	Imaging modality	Abnormal findings
11-4-2021	Brain PET scan	Left encephalomalacia with surrounding gliosis
7-9-2021	CT (chest, neck, abdomen, pelvis)	Chest: mild emphysematous changes mainly at the upper lobes. Neck: right posterolateral para-tracheal air cyst. Abdomen and pelvis: mild thickening of the left adrenal gland (old finding). Hypo-dense lesion at segment VI, measuring up to 0.9*1.3 cm which showed a centri-petal filling on delayed images. Diffuse heterogeneous bone density. Diffuse osteopenia, degenerative changes, and old femoral shaft fracture.
30-11-2021	Whole body protocol (PET+CT)	Head and neck: Left cerebral (temporoparietal) cerebrospinal fluid (CSF) space is seen; indicating old brain insult. Bilateral polypoidal maxillary sinus wall thickening. Chest: small non-specific sub-centimetric mediastinal lymph nodes, for follow-up. Musculoskeletal: Axial and proximal appendicular skeleton: minimal residual bone marrow fluorodeoxyglucose (FDG) uptake. Left shoulder: increased FDG uptake; indicating arthritis. Right mid-femur callous formation; mostly due to previous trauma.
12-1-2022	Chest angiography CT scan (to rule out pulmonary embolism)	Few bilateral foci of consolidation and ground glass opacities. Stable fat density lesion overlying the lower part of the right trapezius muscle. Right para-tracheal cyst (old finding). Diffuse heterogeneous density at the visualized parts of the bone.
3-3-2022	Chest CT scan	mild emphysematous changes, mainly at the upper lobes (old finding).
22-3-2022	CT scan	Picture of pneumonia, and a stable hypo-dense liver lesion.
26-4-2022	Echocardiogram	Mild pericardial effusion.

Based on the patient's medical history, clinical examination, and investigations including histopathologic findings, the diagnosis was Rituximab-induced leukocytoclastic vasculitis. Rituximab treatment was stopped, and the patient started taking steroid therapy. In about two months of rituximab discontinuation, the skin lesions disappeared.

Discussion

Rituximab is an anti-CD20 B-cell chimeric monoclonal antibody medication that is commonly used to treat various forms of cancer, including B-cell chronic lymphoid leukemia and follicular non-Hodgkin's lymphoma. However, like all medications, rituximab can also have unintended side effects. One such side effect is vasculitis, which is a rare but recognized complication of rituximab therapy **[5]**. According to the available literature, our case appears to be the first in the Middle East region and one of the few worldwide cases of biopsy-confirmed rituximab-induced vasculitis.

Here, we present three additional reported unique cases. The first case was a 44-year-old Japanese man who developed vasculitis two days after the first infusion of rituximab, manifesting as a symmetrical, erythematous annular rash on both lower legs **[6]**. The second case was a 67-year-old American woman who developed hemorrhagic bullae on her upper arms, palms, trunk, thighs and legs after the third dose of rituximab **[6]**. The third case was a 38-year-old Korean man with rheumatoid arthritis who developed symmetrical, erythematous patches that later became purpuric lesions one day after receiving the first infusion of rituximab **[4]**.

The exact pathomechanism of rituximab-induced vasculitis is still under debate, but the most accepted explanations involve a rituximab-anti rituximab antibody complex reaction and cytokine release syndrome. The latter is thought to be responsible for the systemic side effects through the release of a massive amount of TNF-α and IL-6, which can change the vessel walls and activate a cascade of reactions, resulting in the formation of true vasculitis **[7]**.

It is important to note that before confirming the diagnosis of rituximab-induced vasculitis, other etiologies must be ruled out. This includes a detailed history taking, physical examination, and laboratory tests to exclude infections, autoimmune diseases, and the usage of other associated drugs. In the cases presented in this report, the patients had no signs of infection, autoimmune diseases, internal organ disorders, or positive autoantibody studies, thus excluding ANCA-associated vasculitis. Furthermore, the patients did not develop symptoms such as myalgia, arthralgia, flushing, or

headache within 24 hours following the first infusion, ruling out an acute infusion reaction **[8,9]**.

Our case report highlights that while rituximab is a widely used treatment option for patients with systemic vasculitis symptoms, it is also a rare but real cause of vasculitis in skin-limited forms. It is important for healthcare providers to be aware of this potential complication and to properly evaluate patients for vasculitis before and during rituximab therapy.

Conclusion

In conclusion, vasculitides are a group of autoimmune conditions that affect blood vessels, and one subtype is cutaneous small-vessel vasculitis. This case report highlights a rare complication of rituximab, which is cutaneous vasculitis. The patient in this case experienced self-limited symptoms that resolved after a few months, but the long-term outcomes and underlying mechanisms of rituximab-induced vasculitis are not well understood. Further research is necessary to gain a better understanding of this side effect and identify any specific risk factors.

References

1. Fraticelli P, Benfaremo D, Gabrielli A. (2021). Diagnosis and management of leukocytoclastic vasculitis. Intern Emerg Med. 16(4):831-841.
2. Micheletti RG, Pagnoux C. (2020). Management of cutaneous vasculitis. Presse Med. 49(3):104033.
3. Antiga E, Verdelli A, Usl A, Centro T, Bonciani D, Bonciolini V. (2023). Drug-induced cutaneous vasculitides. researchgate.net. 63(4):103618
4. Kim MJ, Kim HO, Kim HY, Park YM. (2009). Rituximab-induced vasculitis: A case report and review of the medical published work. J Dermatol.36(5):284-287.
5. Tezer DC, Dogan IG, Arican CD, Demir S, Tutuncu M. (2022). Rituximab-induced leukocytoclastic vasculitis. Neurol Sci Neurophysiol. 39(3):161.
6. Dereure O, Navarro R, Rossi JF, Guilhou JJ. (2001). Rituximab-induced vasculitis. Dermatology. 203(1):83-4.
7. Kandula P, Kouides PA. (2006). Rituximab-Induced Leukocytoclastic Vasculitis: A Case Report. Arch Dermatol. 142(2):246-247.
8. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). 94(7):2217-24.
9. Wooten MD, Jasin HE. (1996). Vasculitis and lymphoproliferative diseases. Semin Arthritis Rheum. 26(2):564-574.

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