Rituximab induced cytokine release syndrome in an MS patient: a case report

Masoud Etemadifar[1], Mehri Salari[2], Mahdieh Saeri[1], Amirhossein Akhavan Sigari[1], and Sara Ebrahimi[1]

[1]Isfahan University of Medical Sciences
[2]Shahid Beheshti University of Medical Sciences

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Abstract

Rituximab use in multiple sclerosis has been promising. Cytokine release syndrome (CRS) is a common side effect of rituximab in patients with lymphoma. We report a case of a 44-year-old man with a history of relapsing-remitting multiple sclerosis, who presented with signs and symptoms consistent with CRS after rituximab initiation.

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Masoud Etemadifar

Professor of Neurology, Department of Neurosurgery, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

Postal Code: 8174673461

Email: etemadifar.1963@gmail.com

Mehri Salari

Assistant Professor of Neurology, Department of Neurology, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Email: mehri.salari@gmail.com

Mahdieh Saeri

Alzahra Research Institute, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

Postal Code: 8174673461

Email: mh.saeri@gmail.com

Amirhossein Akhavan Sigari **(Corresponding author)**

Alzahra Research Institute, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

Postal Code: 8174673461

Tel:00989132151729

Email: amirsigari@aol.com

Sara Ebrahemi

Alzahra Research Institute, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

Email: ebrahemi.sara1368@gmail.com

Key Clinical Message

Cytokine release syndrome with rituximab has been reported in certain diseases, however, it is rarely reported in MS patients treated with rituximab. The treating physician should suspect the syndrome when typical signs and symptoms appear.

Abstract

Rituximab use in multiple sclerosis has been promising. Cytokine release syndrome (CRS) is a common side effect of rituximab in patients with lymphoma. We report a case of a 44-year-old man with a history of relapsing-remitting multiple sclerosis, who presented with signs and symptoms consistent with CRS after rituximab initiation.

Keywords

Multiple sclerosis

Cytokine release syndrome

Rituximab

Background

Multiple sclerosis (MS) is an immune mediated inflammatory disease of the central nervous system (CNS). Lymphocytes play a key role in the pathogenesis of MS. Due to the critical role of B lymphocytes in MS pathology, monoclonal antibodies targeting such cells have been proposed for MS treatment.(1) Rituximab, a monoclonal antibody against CD20 receptors on B lymphocytes, is now being widely used for autoimmune diseases such as MS, rheumatoid arthritis, and cancer therapy, and has had comparable clinical outcomes in managing MS than other injectable and oral disease modifying therapies (DMTs). (2) Therefore, rituximab is being prescribed by medical practitioners for MS therapy in certain countries.(1)

Infections and mild to moderate infusion related reactions are more common side effects of rituximab, and life threatening complications such as anaphylaxis appear to be less frequent. An important side effect of rituximab is cytokine release syndrome (CRS) characterized by rash, fever, mental status changes, etc.(3,4). CRS has been reported in MS patients treated with monoclonal antibodies such as alemtuzumab, however, rituximab induced CRS in MS patients is extremely rare.(5)

Case Presentation

A 44-year-old man with a history of relapsing-remitting multiple sclerosis was referred to our MS Clinic for the evaluation of bilateral edema of the lower limbs. The edema appeared shortly after the patient had received his last rituximab infusion. The patient also complained of headache and generalized arthralgia. Upon physical examination bilateral symmetric pitting edema of the lower limbs was evident, no skin lesions were present, vital signs were stable and patient was not febrile. Lab data revealed an increased serum creatinine level of 1.4 mg/dl, SGPT of 78 U/l (N=6-45), SGOT of 64 U/l (N=8-40), along with a C-reactive protein (CRP) level of 57 mg/dl (N= less than 10 mg/dl).

On 2001 the patient had experienced a right side optic neuritis, one year later he had ataxia and diplopia and magnetic resonance imaging (MRI) of the brain and spinal cord were done, which showed hyperintense lesions at the level of the spinal cord (Figure 1), the patient was diagnosed with MS and interferon-beta 1a was started. 5 years later he had an attack of bilateral lower limb paresis, and 3 years later he experienced

a severe attack of quadriparesis. After the acute management of his attack, the patient's drug was changed to fingolimod. On 2018 when he was on fingolimod for 2 years his drug was changed to rituximab by another neurologist. After the first dose of rituximab he experienced a severe infusion reaction, presented by erythema and urticarial lesions. Two days later he noticed bilateral edema of the lower limbs that had gradually worsened, and somnolence. The patient was evaluated by several specialists regarding his limb edema. His symptoms improved with antihistamines and corticosteroids, but after 6 months, when he receives his second dose of rituximab, he presented again with bilateral limb edema.

Based on the patient's history and by taking into account lab data, cytokine release syndrome was highly suspected. The patient was managed with antihistamines and corticosteroids.

Discussion and Conclusion

One of the main side effects of rituximab are infusion reactions which mainly consist of cytokine release syndrome and in some cases, type I hypersensitivity reaction. (1). Cytokine release syndrome is an overreaction of T lymphocytes that leads to an increased release of certain cytokines (interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, tumor necrosis factor (TNF), and interferon (INF)) especially IL-6. Lab work may reveal azotemia, hyperbilirubinemia, and elevated D-dimer levels. CRS symptoms mainly consist of rash, fever, myalgia, arthralgia, nausea, vomiting, diarrhea, tachycardia, tachypnea, headache, confusion, mental change, and seizure.(6,7). Infection with Covid-19 also induces CRS by massive release of cytokines sometimes stated as a "cytokine storm"(8). Tocilizumab is considered one of the drugs for treating CRS.(9)

In our case, middle aged man who was diagnosed with MS, was started on rituximab. After the first dose the patient had shown signs of CRS, however, due to its rare prevalence, management was done based on a diagnosis of moderate allergic reaction. After the second dose of rituximab the patients had presented with similar symptoms, although more severe.

Neurologic side effects such as mental status changes can appear during or after other signs and symptoms. (10). CRS has been classically associated with therapeutic monoclonal antibody infusions, most notably anti-CD3 (OKT3), anti-CD52 (alemtuzumab), and anti-CD20 (rituximab).(11).

An important differential diagnosis of CRS is capillary leak syndrome, serum sickness (type III hypersensitivity reaction) (12), and idiopathic infusion reaction. Capillary leak syndrome is a massive leakage of fluid into the interstitial space secondary to increased permeability of vessels mediated by released interleukins that leads to sudden hypotension and shock. Other features may include generalized edema, hemoconcentration and hypoalbuminemia. It is mainly seen in patients with sepsis.(4). There are also reports of capillary leak syndrome in NMO patients treated with rituximab(13).

The overlap between CLS and CRS mandates differentiation of these two syndromes when approaching patients. Capillary fluid leakage is seen in both syndromes but the leakage in CLS is so severe that causes hypotension and shock. Cytokine release syndrome mostly starts with fever, rash, and malaise and is rarely associated with shock. However, hypotension can occur in the course of the disease leading to capillary leak syndrome.(7)

Although rituximab induced cytokine release syndrome has been reported in the treatment of certain diseases(13), this syndrome is very rare in MS patients being treated with the drug. Monoclonal antibodies such as rituximab are now being widely used to treat MS and all side effects of the drug should be assessed and differentials should be recognized when adverse effects occur. Therefore cautious use of the drug in this subset of patients is advised.

Abbreviations

MRI: magnetic resonance imaging

CRS: cytokine release syndrome

MS: multiple sclerosis

DMTs: disease-modifying therapies

CLS: capillary leak syndrome

FLAIR: fluid-attenuated inversion recovery

Declaration

Competing interests

The authors have no competing interests to declare.

Consent to publish

Written consent was taken from the patient for the publication of this paper. A copy of the consent form is available for review by the editor of the journal.

Availability of data and materials

Not applicable

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Ethics

Written consent was obtained from the patient for the presentation of this case.

Authors' Contributions

ME, MeS, and MaS provided the case's relevant information, history and images. AAS and SE wrote the primary draft of the manusript. AAS, MeS, ME, MaS wrote the final draft and extracted relevant data from the literature. The final manuscript was read and approved by all of the authors.

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Figure legends :

Figure 1; Fluid-attenuated inversion recovery (FLAIR) cervical spine MRI of the patient revealing a hyperintense lesion at the level of C3-C4.

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