Multiple Sclerosis and Related Disorders 37 (2020) 101429

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Case report

Rituximab associated necrosis: A case report

Fereshteh Ashtari[a], Atousa Hakamifard[b,*], Amirali Hariri[c], Tahereh Gholipour-shahraki[d]

[a] Isfahan Neuroscience Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Infectious Diseases, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[c] School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran
[d] Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

ARTICLE INFO

Keywords:
Rituximab
Necrosis
Devic's syndrome

ABSTRACT

Background: Rituximab is a B-cell-depleting unconjugated monoclonal IgG1 antibody that targets the transmembrane protein CD20. This article reports on a case with the rare complication known as Rituximab-associated mucosal necrosis.
Case presentation: The present case report addresses, for the first time, a patient affected by Devic's syndrome presenting with oral manifestations of palatal necrosis after rituximab treatment.
Conclusion: The present case raises the possibility of anti-CD20 antibody contributing to the development of palatal mucosal necrosis in some patients. Given the increasing administration of rituximab as a result of its efficacy against several diseases, a report on the potential iatrogenic effects of this drug is essential.

1. Introduction

Rituximab is a B-cell-depleting unconjugated monoclonal IgG1 antibody that targets the transmembrane protein CD20 and is only found on the surface of normal and neoplastic B-cells and ultimately depletes circulating B lymphocytes by cell lysis (Thiebaut et al., 2018). Rituximab has been frequently utilized for the treatment of a wide range of autoimmune and malignant diseases (Karmacharya et al., 2015). It was first approved in 1997 for the treatment of non-Hodgkin lymphoma (Rastetter et al., 2004). More recently, the indication for rituximab therapy has increased significantly, especially in the treatment of autoimmune connective tissue diseases, such as Rheumatoid Arthritis (Harrold et al., 2015), SLE (Eriksson, 2005), Sjögren syndrome (Seror et al., 2007) and ANCA-associated vasculitis (Stone et al., 2010). Given the role of B-cells in the pathogenesis of Devic's syndrome and also the role of CD20 depleting drugs, Rituximab is used for the treatment of this disease (Annovazzi et al., 2016). Many studies have shown that rituximab is significantly effective in lowering the number of episodes and stabilization of disability in most treated patients (Cabre et al., 2018). To the researchers' knowledge, there are no data about the adverse effects of rituximab in this population (Damato et al., 2016). In general, rituximab is relatively safe, and most of its adverse reactions are mild. The most common side-effects of this treatment include general infusion reactions, including fever, chills and asthenia, as well as lymphopenia and anaphylactoid reaction. Other reported serious adverse reactions include infection, interstitial lung disease and leukoencephalopathy. The administration of rituximab can also cause mucocutaneous adverse reactions such as rash, urticaria and pemphigus, and, in severe cases, the Steven-Johnson syndrome and toxic epidermal necrosis (Saulite et al., 2018).

The present case report addresses, for the first time, a patient affected by Devic's syndrome presenting with oral manifestations of palatal necrosis after rituximab treatment.

2. Case report

A 30-year-old woman was admitted to the hospital with a two-day history of watery stool or diarrhea, fever and odynophagia. Her medical history included Devic's syndrome and herpetic encephalitis. The patient was under treatment with prednisone and azathioprine. One month later, due to the disease being uncontrolled and the worsening of her symptoms, a course of 2000-mg rituximab was administered. The patient had experienced seven watery stools in the previous 24 h. There was no history of vomiting. A mild abdominal pain was reported. At the time of admission, the patient had a 39 °C body temperature. The laboratory findings revealed a WBC count of 1600 (PMN = 70%), serum creatinine of 2.8, ESR of 86 and CRP of 43. All the other laboratory values were in the normal ranges. Therapy with cefepime and metronidazole then started, and because of the patient's complaints of odynophagia and severe oral thrush, found in the physical examination,

* Corresponding author.
E-mail address: a.hakamifard@med.mui.ac.ir (A. Hakamifard).

https://doi.org/10.1016/j.msard.2019.101429
Received 11 July 2019; Received in revised form 18 September 2019; Accepted 1 October 2019

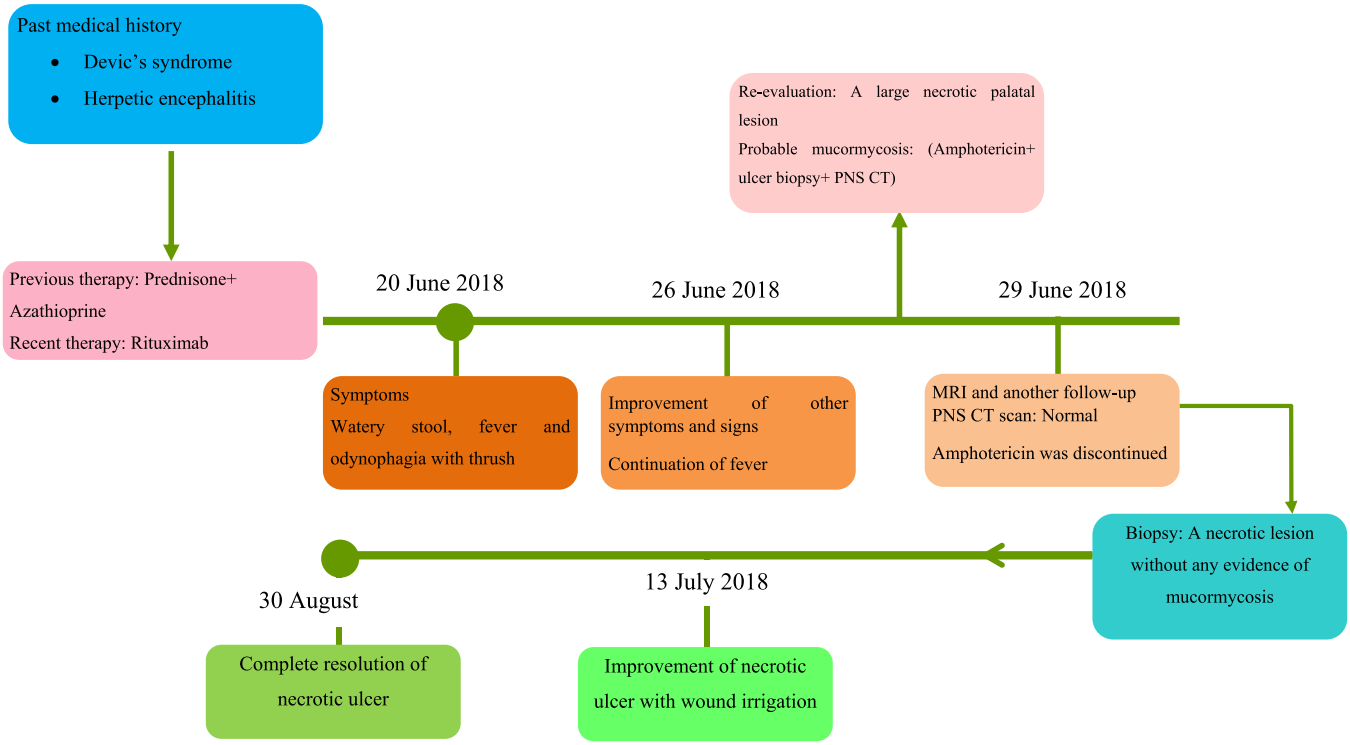

Fig. 1. Timeline. The timeline containing the history, image reports, and interventions provided the time course of the patient we presented.

fluconazole was also administrated. WBC became 3700 (PMN = =78%) the next day. Six days after admission, the patient was febrile, but did not have diarrhea, and the physical examination, ECG, blood culture and abdominopelvic ultrasound did not show remarkable findings. After further evaluation, a large necrotic palatal lesion was observed in the examination. Due to the possibility of mucormycosis given the patient's condition, therapy with empiric amphotericin b liposomal was started and fluconazole was discontinued and a PNS CT scan was requested, but the results came out normal. The patient underwent a biopsy of the palatal necrotic ulcer. After three days of amphotericin administration, MRI and another follow-up PNS CT scan were performed and the results were not remarkable. In the histopathology of the biopsy, only a necrotic lesion without any evidence of mucormycosis was reported; therefore, amphotericin was discontinued. After two months, the patient's oral lesion had been cured with the help of wound irrigation and without any other interventions [Fig 1].

3. Discussion

This case report addresses the unusual case of a 30-year-old woman with possible palatal mucosal necrosis as a potential side-effect of rituximab treatment for uncontrolled neuromyelitis optica. Although previous case reports have described cases of osteonecrosis of the jaws (Keribin et al., 2017; Allegra et al., 2014), a case of nasal skin necrosis (Pearlman et al., 2016), and retinal necrosis as well (Dogra et al., 2018; Schuler et al., 2016), nonetheless, the researchers did find any previous report of mucosal necrosis following rituximab administration. The true etiology of the patient's palatal necrosis remains unclear. Several factors, including the negative action of rituximab on angiogenesis and compromising microvascular, may play a role (Allegra et al., 2014). In the case of this patient, despite the minimal interventions, after approximately eight weeks of local care, the lesion was exfoliated and no significant areas of necrosis remained. Within weeks, the palatal area healed completely without any complications.

In addition to the potentially negative action of rituximab on angiogenesis, another aspect of this case was that the patient was under treatment with azathioprine and prednisone until one month before the initiation of rituximab, and this combination had the potential to induce agranulocytosis and neutropenia (Hadda et al., 2009; Saida et al., 2018). Some case studies have shown that rituximab can itself cause agranulocytosis (Ramesh Amirisetty et al., 2006; Kamei et al., 2015). Agranulocytosis can occur following bone marrow suppression and results from a particular reduction in neutrophil count, referred to as neutropenia. Neutropenia is defined as an absolute neutrophil count of less than 0.5×10^9/L. It can be categorized as mild (count among 1000–1500/˜L), moderate (500–1000/˜L) and severe (less than 500/˜L); in the present case, the WBC count was 1600/L. Neutropenia can also be classified into acute and chronic types. Several studies have proved the effect of neutropenia on the development of oral ulcers, such as gingival lesions (Ramesh Amirisetty et al., 2006), mucosa ulceration (Mortazavi et al., 2016) and opportunistic infections.

Due to the discontinuation of rituximab, the necrotic ulcer improved after two weeks and resolved completely after approximately eight weeks.

To conclude, the present case raises the possibility of anti-CD20 antibody contributing to the development of palatal mucosal necrosis in some patients. Due to the increasing administration of rituximab, it is important to report any potential iatrogenic effects that this drug may have. The conservative management of oral symptoms, during treatment, should be considered and patients have to be evaluated as quickly as possible. Oral examination should be considered before the initiation of this drug.

Declaration of Competing Interest

None.

References

Allegra, A., Oteri, G., Alonci, A., Bacci, F., Penna, G., Minardi, V., et al., 2014. Association of osteonecrosis of the jaws and poems syndrome in a patient assuming rituximab. J. Cranio-Maxillo-Facial Surg. 42 (4), 279–282.
Annovazzi, P., Capobianco, M., Moiola, L., Patti, F., Frau, J., Uccelli, A., et al., 2016.

Rituximab in the treatment of neuromyelitis optica: a multicentre Italian observational study. J. Neurol. 263 (9), 1727–1735.
Cabre, P., Mejdoubi, M., Jeannin, S., Merle, H., Plumelle, Y., Cavillon, G., et al., 2018. Treatment of neuromyelitis optica with rituximab: a 2-year prospective multicenter study. J. Neurol. 265 (4), 917–925.
Damato, V., Evoli, A., Iorio, R., 2016. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. JAMA Neurol. 73 (11), 1342–1348.
Dogra, M., Bajgai, P., Kumar, A., Sharma, A., 2018. Progressive outer retinal necrosis after rituximab and cyclophosphamide therapy. Indian J. Ophthalmol. 66 (4), 591–593.
Eriksson, P., 2005. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. J. Intern. Med. 257 (6), 540–548.
Hadda, V., Pandey, B.D., Gupta, R., Goel, A., 2009. Azathioprine induced pancytopenia: a serious complication. J. Postgrad. Med. 55 (2), 139–140.
Harrold, L.R., Reed, G.W., Shewade, A., Magner, R., Saunders, K.C., John, A., et al., 2015. Effectiveness of rituximab for the treatment of rheumatoid arthritis in patients with prior exposure to anti-TNF: results from the CORRONA registry. J. Rheumatol. 42 (7), 1090–1098.
Kamei, K., Takahashi, M., Fuyama, M., Saida, K., Machida, H., Sato, M., et al., 2015. Rituximab-associated agranulocytosis in children with refractory idiopathic nephrotic syndrome: case series and review of literature. Nephrol. Dial. Transplant. 30 (1), 91–96.
Karmacharya, P., Poudel, D.R., Pathak, R., Donato, A.A., Ghimire, S., Giri, S., et al., 2015. Rituximab-induced serum sickness: a systematic review. Semin. Arthritis Rheum. 45 (3), 334–340.
Keribin, P., Guerrot, D., Jardin, F., Moizan, H., 2017. Osteonecrosis of the jaw in a patient presenting with post-transplantation lymphoproliferative disorder treated with rituximab: a case report. J. Oral Maxillofacial Surg. 75 (12), 2599–2605.
Mortazavi, H., Safi, Y., Baharvand, M., Rahmani, S., 2016. Diagnostic features of common oral ulcerative lesions: an updated decision tree. Int. J. Dent. 2016, 7278925.
Pearlman, A.N., Fechner, F.P., Constantinides, M., 2016. Development of nasal skin necrosis associated with rituximab treatment for Waldenstrom's macroglobulinemia and subsequent spontaneous resolution. Ear Nose Throat J. 85 (7), 431–433.
Ramesh Amirisetty, V.Z., Meenakshi Boddun, Rolly Gupta, Micky Kumari, Hema Suryawanshi. 2006. Treatment emergent agranulocytosis with skin and gingival lesions in a chronic lymphocytic leukemia patient: a case report. 10(10):ZD13–ZD6.
Rastetter, W., Molina, A., White, C.A., 2004. Rituximab: expanding role in therapy for lymphomas and autoimmune diseases. Annu. Rev. Med. 55, 477–503.
Saida, K., Kamei, K., Ogura, M., Matsumura, S., Kano, Y., Sato, M., et al., 2018. Azathioprine-induced agranulocytosis and severe alopecia after kidney transplantation associated with a NUDT15 polymorphism: a case report. Transplant. Proc. 50 (10), 3925–3927.
Saulite, I., Guenova, E., Hoetzenecker, W., 2018. Adverse reactions of antibody-therapy for primary cutaneous lymphomas: rituximab, brentuximab vedotin, alemtuzumab, and mogamulizumab. Curr. Probl. Dermatol. 53, 70–81.
Schuler, S., Brunner, M., Bernauer, W., 2016. Rituximab and acute retinal necrosis in a patient with scleromalacia and rheumatoid arthritis. Ocul. Immunol. Inflamm. 24 (1), 96–98.
Seror, R., Sordet, C., Guillevin, L., Hachulla, E., Masson, C., Ittah, M., et al., 2007. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjogren's syndrome. Ann. Rheum. Dis. 66 (3), 351–357.
Stone, J.H., Merkel, P.A., Spiera, R., Seo, P., Langford, C.A., Hoffman, G.S., et al., 2010. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N. Engl. J. Med. 363 (3), 221–232.
Thiebaut, M., Launay, D., Riviere, S., Mahevas, T., Bellakhal, S., Hachulla, E., et al., 2018. Efficacy and safety of rituximab in systemic sclerosis: french retrospective study and literature review. Autoimmun. Rev. 17 (6), 582–587.