Tumefactive Demyelinating Lesions in a Patient with Multiple Sclerosis Developed two Days after the Injection of Rituximab

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Abstract

Background: Rituximab has been increasingly prescribed in the treatment of multiple sclerosis (MS) over recent years. Tumefactive demyelinating lesions can occur at the onset or over the course of MS. Another major cause of these lesions is the side effects of drugs such as natalizumab or fingolimod. This study is a case report of a young MS patient who suffered from tumefactive lesions following the injection of rituximab.

Case presentation: The patient was an 18-year-old man with MS who developed double vision, imbalance, and quadriparesis symptoms followed by a decrease in his consciousness two days after administration of rituximab. Tumefactive lesions were observed in the patient's brain magnetic resonance imaging (MRI).

Conclusion: Rituximab should be considered as a potential cause of tumefactive demyelinating lesions in patients with MS.

Keywords: Tumefactive demyelinating lesions, Multiple Sclerosis, Rituximab.

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INTRODUCTION

Rituximab is a monoclonal antibody that was initially prescribed in oncological and rheumatic diseases; however, it has been increasingly used in the treatment of multiple sclerosis (MS) over recent years [(1)]. Its beneficial effects on MS treatment have been verified in various studies [(1)]. Hence, its optimal effect, apart from its approximately minor side effects, has resulted in its consideration as an appropriate drug for MS treatment. As B cells have a role in pathogenesis of tumefactive demyelinating lesions, rituximab can be regarded as a potential choice in this respect due to its significant effect on the mentioned cells [(2)]. In the following section, a case diagnosed with MS and treated with rituximab is introduced. However, the mentioned case suffered from tumefactive lesions following the injection of rituximab.

CASE SPECIFICATION

The patient was an 18-year-old man who referred to the MS clinic of Sina hospital in September 2017

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with double vision, imbalance, and quadriparesis. His symptoms initiated three months ago when the patient experienced dizziness, vomiting, and imbalance. Neurological examination performed at that time indicated a horizontal nystagmus in both directions accompanied by imbalance in walking. However, the results provided by other neurological and systemic examinations of the patient were normal. The patient had no history of any previous illnesses and did not consume any specific drug. Moreover, the patient's family history was negative. In the patient's brain magnetic resonance imaging (MRI), demyelinating plaques were observed in the pons, and periventricular and temporal regions (Fig. 1- a, b, c). The results of biochemical, vasculitis, and anti-aquaporin 4 antibody tests were all negative. The patient's cerebrospinal fluid sample revealed that the result of oligoclonal band test with 4 bands was positive. He was treated with pulsed therapy with injectable form of methylprednisolone, 1 g for five days. His symptoms improved, and then rituximab (1 g intravenous injection) was used as the preservative treatment. Two days after the injection, the patient indicated double vision, imbalance, and quadriparesis symptoms followed by a decrease in his consciousness. No specific point was observed in his systemic examination, and the patient did not have fever. In the neurological examination, he opened his eyes with painful irritation and had an inaudible verbal response. The pupils had normal size and were reactive to light. His reflexes increased, and the patient had bilateral Babinski signs. The results of his primary and routine tests were normal. Tumefactive lesions were observed in the patient's brain MRI (Fig. 2- a, b). Once more, the patient was treated with pulsed therapy with injectable form of methylprednisolone, 1 g for five days. His condition improved, and he became conscious. He was discharged afterwards and referred to the MS clinic at Sina hospital. In the referral, he still complained of double vision, imbalance, and weakness of his four organs. The patient had bilateral internuclear ophtalmoplegia (INO) in the examination. The muscle strength of the four organs was reduced to 4/5. He could walk independently, though with lack of balance. Reflexes were increased, and bilateral Babinski signs were observed. Thorough examination of the possible metastatic causes including biochemical

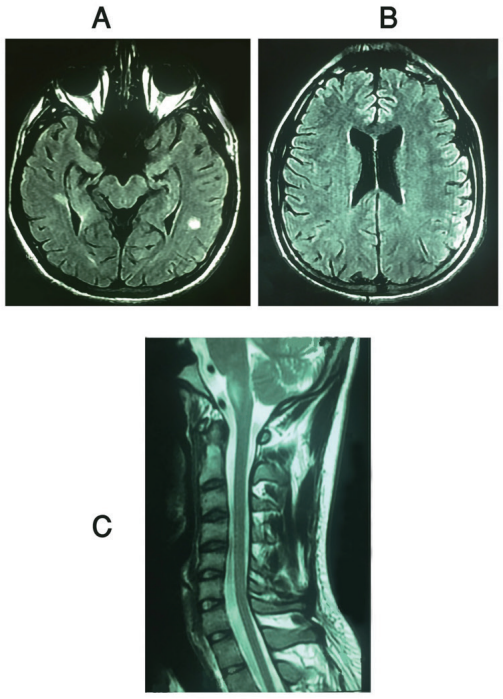

Figure 1. a, b, c. MRI revealed demyelinating plaques in the pons, and temporal and periventricular regions.

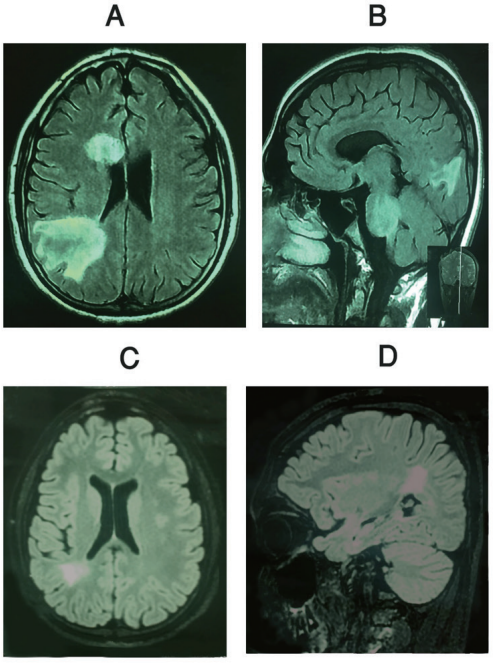

Figure 2. a, b. Brain MRI revealed tumefactive demyelinating lesions. c, d. Follow up MRI showed an obvious recovery.

tests and computed tomography (CT) scan from the lungs, abdomen, and pelvis indicated normal results. The results of vasculitis and anti-aquaporin 4 antibody tests as well as the anti- myelin oligodendrocyte glycoprotein (anti-MOG) antibody examination were all normal. Due to lack of complete improvement and neurological deficiency, he was treated with plasmapheresis for five sessions, each time with two liters replaced by 20% of albumin. His condition significantly improved, and his symptoms were mainly resolved. A monthly injection of 1 g cyclophosphamide was prescribed for the patient. After six months, an MRI was preformed once more, which revealed an obvious recovery (Fig. 2. c, d). His complaints were completely resolved, as well.

DISCUSSION

Tumefactive demyelinating lesions have different causes, one of which is the MS disease itself [2]. These lesions can occur at the onset or over the course of MS. Another major cause of these lesions is side effects of drugs. The mentioned cause of lesions has been particularly reported after consumption of fingolimod and natalizumab [2, 3]. To the best of the author's knowledge, the presented case report is the second case, in whom the tumefactive lesions were developed following the injection of rituximab. The previous case [4] was a 55-year-old man who was treated with rituximab due to recurrence of the disease in spite of consuming drugs such as glatiramer acetate, cyclophosphamide, and natalizumab. Six weeks after the fifth injection of rituximab, the patient indicated tumefactive lesions in the right parietal lobe and was treated with alemtuzumab after performing extensive examinations.

Our patient, however, suffered from tumefactive lesions right after the injection of rituximab. The observed tumefactive lesions can be attributed to the disease course itself. TDLs is not uncommon in the course of MS. The patient has had a relapse 3 months ago. Thereafter, exacerbation of disease manifested by TDLs should be considered in mind. On the other hand, the role of rituximab in their development is highly probable given that they occurred exactly after the injection of rituximab.

The possible involvement of rituximab in the development of these lesions is justifiable considering two mechanisms. The first is the effect of T cells. As known, the effect of rituximab is initiated by destroying B cells. Such a rapid action in destroying B cells can, in effect, result in an abrupt increase in the number of T cells and thus cause brain lesions.

The second justification is attributed to the role of an anti-rituximab antibody. The effects of antibodies against anti-monoclonal antibodies have been more pronounced after consumption of natalizumab[5]. It has been specified that in the first six months after consumption of natalizumab, antibodies may become present in the blood in 9% of cases, which in turn reduces the effectiveness of the consumed drug. Moreover, in some cases, it can even reduce the level of natalizumab to zero [5]. In tumefactive lesions caused by natalizumab, it is suggested that these lesions may either occur due to ineffectiveness of natalizumab in the presence of antibodies or due to the role of antibody itself in directly contributing to the development of these lesions [5]. Probably, the same mechanism may be involved regarding rituximab and its resulted tumefactive lesions. However, although the number of studies addressing anti-rituximab antibodies is few, they have indicate that unlike the antibodies that are against rituximab, the presence of this antibody is not associated with clinical symptoms [6]. Therefore, with respect to the mentioned patient, the direct effect of the antibody on the brain tissue can justify the observed symptoms. Unfortunately, as it was not feasible to measure the antibodies in the present study, we cannot definitely answer the raised question. The results obtained from the present study suggest that tumefactive lesions can have a very complex pathophysiology, contrary to the assumed assumption; these lesions are not only developed in response to consumption of drugs affecting T cells, but also can be developed due to the effect of drugs which reduce B cells. Examination of more cases as well as conduction of more precise laboratory tests can shed better light on various aspects of the development of these lesions.

In addition to the above mentioned explanation, reversible posterior leukoencephalopathy syndrome (RPLS) should be considered as a differential diagnosis of tumefactive demyelinating lesion in a patient receiving rituximab. RPLS has been reported as a complication of rituximab [7]. However, the asymmetric involvement of

brain and the areas of involvement in MRI after receiving rituximab, makes the diagnosis of RPLS difficult.

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