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Course of neuromyelitis optica during inadvertent pregnancy in a patient treated with rituximab

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In neuromyelitis optica (NMO), the monoclonal B-cell antibody rituximab is a therapeutic option. Little is known about the course of NMO and the safety of rituximab during pregnancy. In this study, we report the clinical course of a patient with NMO after application of rituximab 1 week before inadvertent conception. Mother and child did not experience any adverse event, and the post-partum development of the baby was completely normal up to 15 months. Clinical course of NMO was stable during the entire pregnancy. This case illustrates a favorable outcome in a pregnant NMO patient and her child after therapy with rituximab. *Multiple Sclerosis* 2009; **15:** 1006–1008. http://msj.sagepub.com

Key words: devic's disease; neuromyelitis; optica; pregnancy; rituximab

Introduction

Neuromyelitis optica (NMO) is an inflammatory disorder of the central nervous system that is classically restricted to the optic nerves and spinal cord. New histopathological and serological findings point to a pathogenic role of serum autoantibodies directed against the aquaporin-4 (AQP4) water channel. Treatment usually relies on immunosuppressant medications, such as azathioprine, mitoxantrone, mycophenolate mofetil, and more recently, rituximab, a monoclonal anti-CD20+ B-cell antibody [1].

Little is known about the course of NMO and the safety of rituximab during pregnancy. Although the substance had not shown fetotoxicity in nonhuman primates, human data are limited. There are only a few case reports on the effects of rituximab during pregnancy in patients with B-cell lymphoma who generally had a favorable outcome of their pregnancy despite rituximab treatment. Because rituximab is a chimeric antibody of the IgG isotype, it crosses the placenta from week 16 onwards and, therefore, may deplete B-cells of both mother and child [2].

In this study, we report the clinical course of NMO in a pregnant woman who received rituximab 1 week before inadvertent conception.

Case report

This previously healthy 19-year-old woman developed optic neuritis and myelitis in 2001. Cerebrospinal fluid investigations revealed eight lymphocytes/μL and elevated protein (78 mg/dL) without oligoclonal banding. IgG titer to measles, rubella, and varicella zoster, (MRZ reaction) were within normal range. Magnetic resonance imaging (MRI) of the spinal cord showed an extensive T2-hyperintensive lesion extending over five vertebral segments, whereas the cranial MRI was completely normal. NMO was diagnosed according to the diagnostic criteria of Wingerchuk, *et al*. [3]. Subsequently she was tested positive for AQP4-abs.

After initial stabilization during 5 years of therapy with azathioprine, she experienced several relapses in 2006. At this time she had a persistent visual deficit on the right eye (visual acuity right eye 0.63, left eye 1.3), a moderate paraparesis and a marked decrease in proprioception (EDSS 4.5). Azathioprine was discontinued, and treatment with rituximab was started in February and March 2007 (1 g rituximab twice with a 2-week interval). Rituximab led to complete depletion of CD19+ B-cells (Figure 1). Four weeks later, the patient had a positive pregnancy test. The date of her inadvertent

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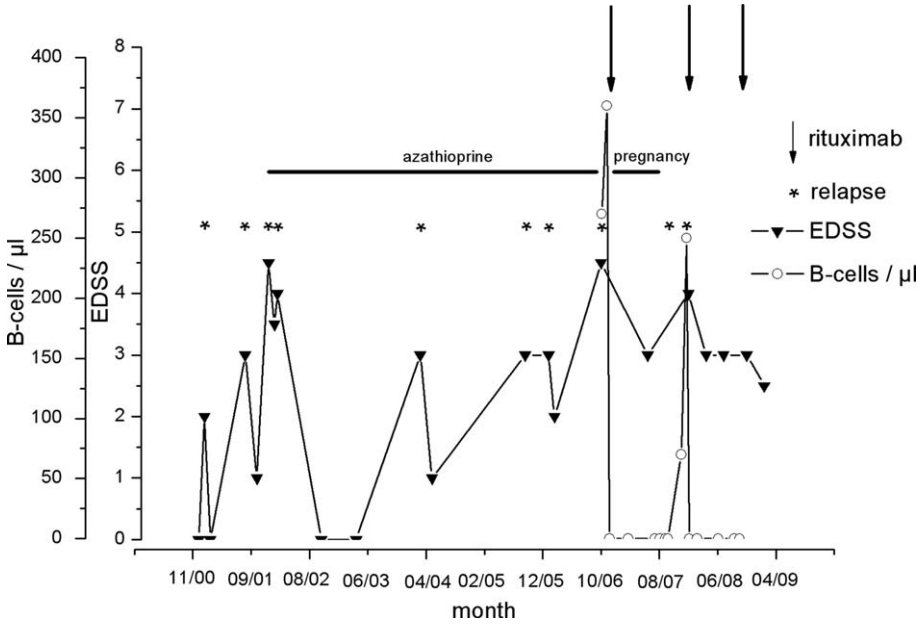

Figure 1 This figure shows EDSS-score, B cells, and relapses (*) since disease onset. Application of rituximab (arrows) led to B cell depletion. One relapse occured one week after delivery despite lasting depletion of B cells.

conception was determined as 1 week after the second rituximab infusion.

CD19+ B-cells remained depleted, and the clinical course was stable during the entire pregnancy. Fetal development was regularly monitored and was normal during pregnancy. At delivery on December 25, 2007, B-cells were still absent in the mother, whereas the child had completely normal B-cell counts. Serum IgG levels of mother and child were within normal limits. All clinical examinations of the newborn were normal; routine vaccinations could be given without side effects. Ten days postpartum, the mother had a new relapse of myelitis. CD19+ B-cells were not detectable at this time point. Treatment with high-dose corticosteroids was followed by remission of her symptoms. Two months later, she had another relapse. CD19+ B-cells were detectable again, and a second course of rituximab was given in April 2008 (two times, 1 g two weeks apart). The patient has remained stable until now (Figure 1). Further development of the baby was completely normal.

Discussion

Because NMO is rare, data on course and outcome of pregnancies of NMO patients are limited to a few case reports [4]. All previously described patients had severe exacerbations of NMO during pregnancy. It is known that pregnancy leads to a progressive shift from Th1-mediated immune response to increased Th2-mediated immunity [5] due to increasing levels of progesterone and estrogens. This could explain why pregnancy ameliorates some autoimmune diseases such as multiple sclerosis (MS) or rheumatoid arthritis (RA) [6,7], whereas others, such as systemic lupus erythematodes; mainly mediated by Th2 cytokines, have an unpredictable course or tend to worsen during pregnancy [8]. In contrast to the previously reported patients with NMO who all experienced marked disease exacerbation, our patient remained completely stable during pregnancy after treatment with rituximab just before inadvertent conception.

Treatment of autoimmune diseases during pregnancy and during the postpartum period is challenging. Corticosteroids and some immunosuppressive drugs (e.g., azathioprine) are used, but may be associated with complications such as preterm delivery, low birth weight, and intrauterine growth restriction [9]. Data on the safety of rituximab during pregnancy are very limited. The Food and Drug Administration classification is category C (risk cannot be ruled out). In our patient, application of rituximab 1–2 weeks before conception was followed by clinical stabilization of her NMO during the entire pregnancy and was not associated with any abnormalities of the child.

Data on the postpartum course of NMO are also lacking. In MS as well as in RA, the risk of relapse is increased during the first months after delivery [7]. Postpartum application of intravenous immunoglobulins (IVIg) has been recommended for patients with high risk of MS [6]. However, the benefit of

IVIg in MS remains doubtful [10]. Our patient had a relapse just 1 week after delivery despite lasting depletion of her B–cells, 9 months after treatment with rituximab. This indicates that other B-cell independent mechanisms, such as proinflammatory mediators or other types of immune cells, might contribute to disease activity in patients with NMO during the postpartum period. Whether patients with NMO would also benefit from postpartum IVIg prophylaxis is currently unknown.

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