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Case report

Initiation of rituximab therapy for new onset neuromyelitis optica spectrum disorder during pregnancy

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ABSTRACT

Background: Aquaporin-4 IgG (AQ4-IgG)-neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory CNS disease that is predominantly characterized by severe relapses of optic neuritis and longitudinally extensive transverse myelitis (LETM). Women are disproportionately affected by AQ4-NMOSD, usually with disease onset occurring between the ages of 35–45. This has significant implications during pregnancy, as disease activity in NMOSD does not remit during gestation. The optimal treatment of NMOSD during pregnancy has not been established.

Methods: Case report.

Results: A 35-year old woman, 10 weeks pregnant, presented with bilateral optic neuritis and intractable hiccups. Workup revealed seropositive aquaporin-4 IgG. She was treated with pulse intravenous methylprednisolone and plasma exchange. Because of high risk for future relapse, Rituximab 1000 mg was given at weeks 15 and 17 of pregnancy. She had no further relapses during pregnancy. She delivered her daughter at 39 weeks without complication.

Conclusion: This case demonstrated a favorable outcome in administering rituximab for NMOSD with disease onset during pregnancy. This description of therapy for disease onset during pregnancy is novel, and adds to the few existing case reports of administering rituximab during pregnancy.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory CNS disease that is predominantly characterized by severe relapses of optic neuritis and longitudinally extensive transverse myelitis (LETM), but also can involve the brainstem, diencephalon, and cerebral hemispheres (Wingerchuk et al., 2015). In over 75% of patients with NMOSD, pathogenic antibody to astrocyte-associated aquaporin-4 (AQ4-IgG) is detected in serum (Wingerchuk et al., 2015). AQ4-IgG seropositivity confers a significantly elevated risk of disease relapse within 12 months of presentation, up to 60% in patients presenting with LETM (Wingerchuk et al., 2015).

Women are disproportionately affected by AQ4-NMOSD compared with men by a ratio of 3.6:1–10.1:1, usually with disease onset occurring between the ages of 35–45 (Zekeridou and Lennon, 2015). This has significant implications when contemplating pregnancy, as disease activity in NMOSD, unlike in multiple sclerosis (MS), does not remit during pregnancy (Klawiter et al., 2017). Similar to MS, there is increased risk of postpartum relapse in NMOSD (Klawiter et al., 2017). Moreover, pregnant women with NMOSD may have independently increased risks of miscarriage and pre-eclampsia, possibly related to placental expression of AQ4 (Klawiter et al., 2017; Nour et al., 2016). Treatment of AQ4-NMOSD with B-cell depletion has become the standard of care in most specialty clinics. There is increasing evidence supporting the use of rituximab in women with both MS and NMOSD prior to pregnancy to prevent disease activity during pregnancy and postpartum, while timing dosing to minimize exposure to the fetus (Das et al., 2018). However, there is limited information regarding the use of rituximab in NMOSD during pregnancy (Das et al., 2018; Miranda-Acuña et al., 2019).

Herein, we present a case of AQ4-NMOSD with disease onset during the first trimester of pregnancy, ultimately treated with rituximab during the second trimester.

2. Case presentation

A 35 year old woman, 10 weeks pregnant, and without significant past medical history, was admitted to our neurology service after she presented with 2 weeks of intractable hiccups, 1 week of bilateral eye movement pain, and 3 days of progressive bilateral visual loss. She did

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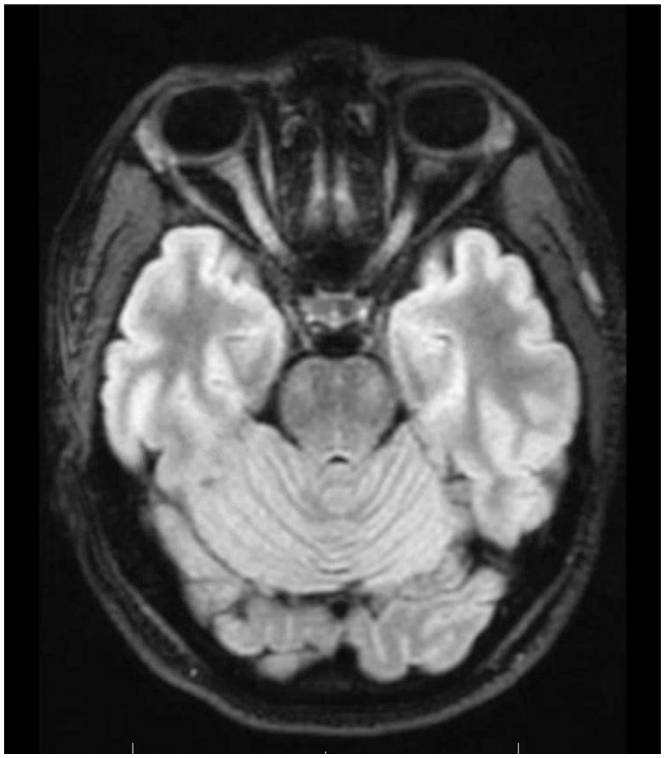

Fig. 1. T2 weighted axial MRI without contrast, demonstrating mildly increased T2 signal intensity within the bilateral optic nerves.

not have any nausea or vomiting. Exam was notable for visual acuity of finger counting only bilaterally, right afferent pupillary defect, and normal fundoscopy. MRI of the orbits without contrast was notable for high T2 signal within the intraorbital portions of both optic nerves, consistent with bilateral optic neuritis (Fig. 1). Brain MRI with T2-weighted thin slices of the brainstem did not show any abnormalities, including the area postrema. No abnormalities were seen on the MRI of the cervical cord. CSF revealed 6 WBCs (81% lymphocytes, normal range 0–5 cells), 1 RBC (normal 0), protein 21 mg/dL (normal range 15–45 mg/dL), glucose 79 mg/dL (normal range 50–80 mg/dL), and 0 oligoclonal bands (normal range 0–1). Given her history of refractory hiccups and severe bilateral optic neuritis, NMOSD was suspected. After discussing the risks and benefits of IV steroids in the first trimester of pregnancy with maternal-fetal medicine, most notably a potentially increased risk of cleft palate (Bandoli et al., 2017-08-01), she was started on intravenous methylprednisolone 1000 mg daily for five days. Because of only minimal improvement on steroids, she underwent 5 sessions of plasma exchange. Her first plasma exchange session occurred the day after her fifth and final day of IV steroids. During plasma exchange she continued steroids in the form of oral prednisone 60 mg for four days, followed by 30 mg for four days before she was discharged on 20 mg daily. After the third plasma exchange session her visual acuity had improved to 20/70 and OS 20/30, and after completion of the fifth plasma exchange session her visual acuity improved to 20/40 OD and 20/25 OS. Serum aquaporin-4 IgG subsequently returned positive (no titer reported).

Following another discussion with the patient and maternal-fetal medicine, which included the increased risk of miscarriage associated with NMOSD and the risks and benefits of pursuing disease modifying therapy during pregnancy, it was decided to initiate rituximab. Rituximab 1000 mg was given at both weeks 15 and 17 of pregnancy, without complication. Prednisone 20 mg daily was tapered and discontinued after her second rituximab infusion, and she was treated with daily aspirin 81 mg for pre-eclampsia prophylaxis. The remainder of her pregnancy and delivery was uncomplicated. She delivered her daughter at 39 weeks via spontaneous vaginal delivery, with APGARs 9 at 1 min and 9 at 5 min. The baby weighed 3320 g. Delivery was only complicated by second degree perineal lacerations. The infant's B-cell count at one month was normal (Table 1). Unfortunately cord blood was not obtained at birth. The patient breastfed her child until the next scheduled rituximab infusions, at 4 weeks and 6 weeks postpartum. The patient opted to stop breastfeeding before the second rituximab cycle. At the time of this submission, the baby was nine months old, and had demonstrated normal growth milestones and there were no infectious concerns.

3. Discussion

This case demonstrated a favorable outcome in administering rituximab for NMOSD with disease onset during pregnancy. It is not exceedingly rare for NMOSD to initially present during pregnancy. In a survey completed by Klawiter et al., of 172 women with a history of both NMOSD and pregnancy, 6 women had their initial symptom onset during pregnancy (Klawiter et al., 2017). The same study found that, compared to the 2 years leading up to pregnancy, the annualized relapse rate increased significantly during the first trimester from 0.17 to 0.73 and during the first three months postpartum from 0.17 to 1.33 (Klawiter et al., 2017). Notably relevant to our patient, there were three survey responders who experienced a relapse both during pregnancy and within 9 months postpartum of the same pregnancy. These data highlight the concern that pregnancy is not protective against NMOSD relapses; relapses continue during pregnancy, and relapse risk increases

Table 1
Lymphocyte counts of mother and daughter. Normal lab ranges are provided within the parentheses. Bolded lab values are below the lower limits of normal range. The mother's post rituximab cycle #1 labs were drawn within hours of completing the second infusion, at 17 weeks gestational age. The mother's pre-rituximab cycle #2 labs were drawn 5 days prior to delivering her daughter, which was 5 weeks prior to the second cycle of infusions. Unfortunately cord blood was not obtained at birth, this would be helpful information in any future cases reported.

	Mother (post-rituximab cycle #1)	Mother (pre- rituximab cycle #2)	Daughter (age 1 month)
T Lymph% (CD3)	62 (54–87)	75 (54–87)	59 (48–85)
T Lymph # cells/uL (CD3)	1041 (754–2810)	1173 (754–2810)	4001 (2300–7000)
CD4%	42 (32–71)	56 (32–71)	43 (33–68)
CD4 # cells/uL	715 (496–2186)	907 (496–2186)	2962 (1400–5300)
T Supress% (CD8)	20 (10–38)	16 (10–38)	14 (9–26)
CD8 # cells/uL	332 (177–1137)	265 (177–1137)	973 (400–2200)
B Lymph% (CD19)	**0 (7–36)**	**0 (7–36)**	22 (4–39)
B Lymph # cells/uL (CD19)	**4 (120–725)**	**1 (120–725)**	1487 (600–3000)
CD4/CD8	2.2 (0.7–3.0)	3.4 (0.7–3.0)	3.0 (0.7–3.0)
NK Lymph% (CD16 + +56)	37 (4–26)	22 (4–26)	17 (2–23)
NK Lymph # cells/uL (CD16 + +56)	609 (37–758)	335 (37–758)	1164 (100–1400)
NK Lymph% (CD3 + +16 + +56)	8	7	1
NK Lymph # cells/uL (CD3 + +16 + +56)	133	102	49

postpartum.

Additionally, there appears to be an association between miscarriages and NMOSD activity. There is an increased risk of miscarriage if there is an NMOSD relapse either during pregnancy or even in 9 months leading up to conception (Nour et al., 2016). AQ4 antibodies in blood may affect placental integrity through interaction with placental AQ4 receptors, which may lead to the reported increased risk of miscarriage and pre-eclampsia seen in NMOSD (Klawiter et al., 2017; Nour et al., 2016).

Given the risk of disease relapse during the remainder of pregnancy and postpartum, and the increased risk of miscarriage associated with disease activity during pregnancy, the patient and medical team decided to initiate rituximab. Our patient was able to carry her pregnancy to term, and did not develop any further relapses either during pregnancy or by nine months postpartum at the time of submission. There was no apparent teratogenicity or increased rate of infections for the baby at nine months of age. Unfortunately, lymphocyte counts were not collected at birth, so our earliest lymphocyte data from baby came at 1 month of age; these were reassuringly within normal ranges. It would have been helpful to collect a cord CD19 count, to look for evidence of B-cell depletion due to in utero exposure to rituximab. This would have informed a better understanding of neonatal immunity, with implications on infant risk of infection and efficacy of vaccinations.

As presented above, the patient elected to stop breastfeeding after the second cycle of rituximab infusions. The American College of Obstetricians and Gynecologists opines that in general, immunomodulating drugs that are not contraindicated in pregnancy are compatible with breastfeeding. However they note there is little data regarding the obstetric and teratogenic risks regarding rituximab, and the lactation risks have not been studied and can't yet be inferred (ACOG Committee Opinion No.776 2019 Apr).

A case series review of women with MS or NMOSD exposed to rituximab within 6 months of conception did not demonstrate major adverse effects on pregnancy higher than that of the general population (Das et al., 2018). There was a recent report of rituximab being continued during pregnancy for treatment of NMOSD in a woman with a history of severe postpartum relapses (Miranda-Acuña et al., 2019).This case similarly did not demonstrate adverse events for either the mother or child. While these cases are encouraging, a larger cohort will be needed to adequately assess whether rituximab represents a safe option to treat NMOSD during pregnancy.

Financial Disclosures

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CRediT authorship contribution statement

Kathleen C. Munger: Data curation, Writing - original draft, Writing - review & editing. **Lawrence M. Samkoff:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Conflicts of Interest

None.

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