

Severe Neuroinflammatory Relapse after Extrauterine Pregnancy and Abortion: A Case Report on a Patient with Heterogenic MS Phenotype Carrying Myelin Oligodendrocyte Glycoprotein Autoantibodies

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Case report

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Abstract

Background. Pregnancy has disease-modifying effects in MS. First trimester abortion might be followed by increased MS activity. MS with myelin oligodendrocyte glycoprotein (MOG) autoantibodies is a rare and aggressive disease variant.

Objectives. This case illustrates severe inflammatory reactivation after surgical abortion in MS patient who carries MOG antibodies.

Methods. Case-report. Patient provided written informed consent for information and images to be published.

Results. MRI and CSF biomarkers indicated high inflammatory activity post-abortion.

Conclusions. Pregnancy termination in combination with MOG antibody carriership and termination of dimethyl fumarate treatment just prior abortion have had contributed to extensive reactivation of MS.

Background

In women with multiple sclerosis (MS), relapse frequency declines during pregnancy, particularly during the third trimester. After delivery, the relapse rate is higher than before pregnancy in the first three months, and eventually decreases to the baseline level.(1)The effects of abortion on MS are not completely understood. A recent study by Landi et al. showed that abortion was associated with a clinical and radiological rebound effect 12 months post-event.(2)Here, we review a case of a 43-year-old woman who developed a drastic neuroinflammatory rebound after an extrauterine pregnancy and a laparoscopic abortion.

Materials And Methods

A woman born in 1976 in the Middle East and moved to Sweden in 2007 was diagnosed with MS in 2010. Patient was enrolled in to STOPMS-II study. Study was approved by Regional Ethical Committee in Stockholm ethical permit DNr 2009/2017-31/2 "STOPMS-II". Patient signed informed consent to participate in this study and patient provided written informed consent for clinical information and images to be published. In her medical history, she had a conservatively treated meningioma, hypertension and gastroesophageal reflux disease. She had no known heredity for neurological diseases. She first presented with optic neuritis in 2008, during her first pregnancy. McDonalds diagnostic criteria 2005 were fulfilled.(3)A myelin oligodendrocyte glycoprotein (MOG) antibody test was not available at that time. Brain MRI just prior to MS diagnosis showed nine T2 lesions and MRI of the spinal cord showed 2 short myelitis lesions. At 2013 brain and spinal cord MRI showed pictures typical for MS with multiple short myelitis lesions. Until 2015, no radiological findings supported a diagnosis other than MS, as no longitudinally extensive myelites were found.

During the period 2011-2014 patient was treated with interferon beta-1a, Expanded disability status scale (EDSS) was 4.0 (2011). The treatment was changed to dimethyl fumarate (DMF) in 2014, due to relapses and new MRI lesions. MRI of brain and spinal cord showed no new lesions, while treated with half dose of DMF during the period January 2015 – April 2019. The DMF treatment was discontinued in August 2019, as the MRI had not shown any new lesions between April 2018 and April 2019, and the patient was considered to have a secondary-progressive disease course with EDSS 7.5. In addition to impaired gait, she also had urinary incontinence, dysphagia and reduced vision, as well as pseudobulbar affects.

In August 2019, the patient sought emergency care for lower abdominal pain and vaginal bleeding. She was diagnosed with tubal pregnancy, with increased levels of serum chorionic gonadotropin 7600 IE/L, indicating pregnancy at week 6. A salpingectomy was performed with no gynaecological complications.

A month before the abortion, the patient had experienced a worsening of her gait: she could no longer take any steps or stand up without falling. The EDSS was 8.0.

Results

MRI in November 2019 showed 8 new gadolinium enhancing (Gd+) lesions and over 50 new T2 lesions in the brain (Figure 1), Gd+ lesions in the spinal cord at levels C2-C3, C5-C7, Th4-Th6, Th8/9, Th11-12.

A CSF analysis was performed and showed a normal count of leukocytes at $5 \times 10^6/L$, very high levels of neurofilament light (NFL) at 13700 ng/L and the presence of MOG antibodies (Table 1). Paradoxically, oligoclonal bands (OCB) in CSF had turned positive in 2019.

Table 1. Cerebrospinal fluid analyses in 2010 and in 2019

Analysis (unit)	2010 May	2019 November	Reference interval
Csf-Albumin (mg/L)	296	351	<280*, <320**
Csf/S-Albumin ratio ()	7.0	10.0	<7.0
Csf-IgG (mg/L)	56	56	<45
Csf-IgG-index	0.58	0.48	<0.70
Csf-leukocytes (/L)	NA	5	0-5
Csf-erythrocytes (/L)	NA	1	<1
Csf-FLC-K (mg/L)	NA	1.24	<0.34
Csf-KFLC-IF	NA	0.35	<0.00
Csf-Aquaporin-4-antibodies	NA	negative	negative
Csf-NFL (ng/L)	NA	13 700	<890
Csf MOG-antibodies	NA	positive	negative
Csf-OCB	absent	present	absent
Csf-CXCL13	NA	33	<7.8

Abbreviations: Ig = immunoglobulin; IL= interleukin; FLC-K = Free light chains type kappa; KFLC = Kappa free light chains; NFL = Neurofilament light; MOG = Myelin oligodendrocyte glycoprotein; OCB = oligoclonal bands; CXCL = Chemokine (C-X-C motif) ligand; mg = milligram; L = liter; ng = nanogram; NA = Not available.

*Reference values in 2010.

**Reference values in 2019

Discussion

In the study by Landi et al., the effects of abortion on MS inflammatory reactivation burden were less pronounced compared to our case.(2)The mean number of post-abortion contrast-enhancing lesions was 0.77 ± 1.40 while the number in preconception MRI scan was 0.39 ± 1.04 ($p=0.004$). (2) However, patients in that study differ from our patient - most of the abortions were spontaneous, the mean EDSS score was under 1.50 and all included patients had relapsing-remitting MS.(3)It is unclear which characteristics of our case made her more vulnerable to the effects of early pregnancy abortion, but heterogenic MS phenotype with MOG antibody presence, EDSS 7.5, disease worsening shortly before the abortion, progressive disease, ortermination of disease modifying treatment (DMT) a week before abortion could affect the outcome. Indeed, the study by Landi et al. also reported higher risk of relapse in patients with more active disease before the conception.Elective abortion was also associated with greater relapse risk

compared to spontaneous abortion. According to the study discontinuation of DMT prior pregnancy termination, increases relapse rate post abortion.(2) Moreover, stressful life events have been associated with risk of exacerbations in MS.(4) Extrauterine pregnancy with a subsequent abortion and surgery might be especially stressful for patients, and surgery can worsen physiological stress(5). Patients with clinical definite diagnosis of MS that carry MOG antibodies are reported to have severe disease course with high relapse rates.(5)

Normal early pregnancy presents a pro-inflammatory stage, whereas many anti-inflammatory mechanisms are active during late pregnancy, causing remission in especially T helper cell (Th)1 and Th17-type autoimmune disorders, including MS. During the transition from late pregnancy to the postpartum period the immune system goes through major changes, often causing relapse in Th1 and Th17 type autoimmune disorders.(6) Immune changes following early pregnancy termination are not well characterised, but early pregnancy pro-inflammatory stage together with immune activation resembling transition to the postpartum stage could have drastic immunological effects in susceptible individuals. Indeed, in the study by Landi et al., length of the pregnancy was inversely associated with the risk of relapse, suggesting a mechanism related to early pregnancy immune activation.(2) Peripheral pro-inflammatory cytokine interleukin-6 (IL-6) was found to be significantly increased in women with tubal ectopic pregnancy compared to intrauterine abortion and normal pregnancy. (7) IL-6 is predictor of tubal ectopic pregnancy with moderate accuracy. (7) IL-6 amplifies IL-17 production in MS patient's T cells in vitro(8). CSF levels of IL-17A correlates with extent of blood-brain barrier damage in relapsing remitting MS. (9) Further, oestrogen has anti-inflammatory and neuroprotective effects in the central nervous system (CNS).(10, 11) Oestrogen levels start to rise in very early pregnancy and a consequent drop in the levels might cause greater relapse rates postpartum in MS.(11)

Conclusions

Abortion is an inflammatory burden modifying event in MS. However, MS with MOG autoantibodies and MOG antibody disease (AD) are rare nosological entities, no studies are available on the effect of preterm termination of pregnancy on these neuroinflammatory diseases. Termination of DMT just prior to abortion might be an unfavourable event that increases risk and severity of inflammatory rebound post abortion. Thus, MOG role in pathogenesis of inflammatory rebound post preterm pregnancy termination in MS and MOG-AD needs to be mapped in future trials.

Abbreviations

CSF Cerebrospinal fluid

CXCL Chemokine (C-X-C motif) ligand;

EDSS Expanded disability status scale

DMF Dimethyl fumarate

Gd+ Gadolinium enhancing

Ig Immunoglobulin

IL Interleukin

FLC-K Free light chains type kappa

KFLC Kappa free light chains

L Liter

NA Not available

NFL Neurofilament light

ng Nanogram

mg Milligram

MOG Myelin oligodendrocyte glycoprotein

MOG-AD MOG antibody disease

MS Multiple Sclerosis

OCB oligoclonal bands

Declarations

Ethics approval and consent to participate. Study was approved by Regional Ethical Committee in Stockholm ethical permit DNr 2009/2017-31/2 "STOPMS-II". Patient signed informed consent to participate in this study.

Consent for publication. Patient signed consent to publish MRI images and clinical data in this publication.

Availability of data and materials. All data generated or analysed during this study are included in this published article.

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Authors' information. NA

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Figures

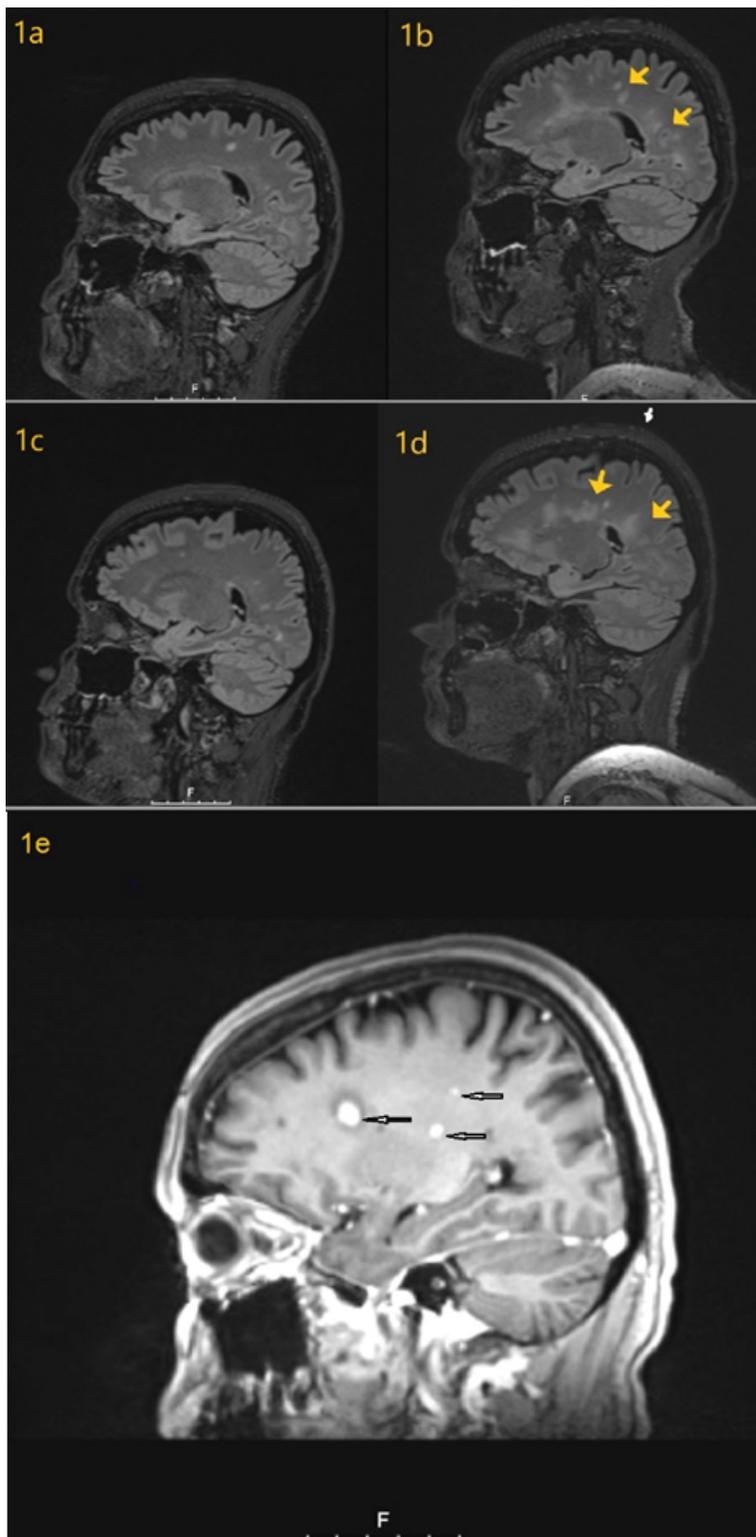


Figure 1

Brain MRI sequences prior and post abortion. Images 1a, 1b. Brain MRI, 3D T2-weighted FLAIR sequences, sagittal image 73 (out of 176) demonstrating radical increase in brain contrast number of T2 lesions between April (1a) and November 2019 (1b, bright arrows). 1c, 1d: 3D T2-weighted FLAIR sequences, sagittal image 109 (out of 176) demonstrating radical increase in brain contrast number of T2 lesions between April (1c) and November 2019 (1d, bright arrows). 1e: 3D T1 weighted sequences with

GBCA (gadolinium based contrast agent) November 2019, showing 3 gadolinium enhancing lesions (1e, black outlined arrows) on sagittal image 50 (out of 76).