Natalizumab and the Risk of PML

Gloria von Geldern, MD
Multiple Sclerosis Center
Assistant Professor of Neurology
University of Washington
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Conflict of Interest

Dr. von Geldern has nothing to disclose.
Instructional Objectives

- Improve ability to diagnose PML in patients with MS
- Review risk factors for development of natalizumab-related PML
- Understand current treatment of natalizumab-related PML
38 y/o woman with relapsing-remitting multiple sclerosis

diagnosed 4 years prior after left optic neuritis
and an episode of sensory changes
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initially started on Copaxone but multiple relapses
now on natalizumab (Tysabri) for 14 months with only 1 relapse
38 y/o woman with relapsing-remitting multiple sclerosis

diagnosed 4 years prior after left optic neuritis
and an episode of sensory changes

initially started on Copaxone but multiple relapses
now on natalizumab (Tysabri) for 14 months with only 1 relapse

presents with progressive aphasia, confusion,
and mild right-sided weakness over several days
Axial FLAIR

Axial T1 post-Gd
CSF

1 RBC, 3 WBC, protein 35, glucose 55
PCR for JC virus positive (3630 copies/mL)
CSF
1 RBC, 3 WBC, protein 35, glucose 55
PCR for JC virus positive (3630 copies/mL)

Diagnosis: PML
Progressive Multifocal Leukoencephalopathy (PML)

Rare, but severe and life-threatening brain infection caused by reactivation of JC virus

Progressive neurological symptoms that need to be distinguished from MS relapse

Diagnosed by MRI and JCV in CSF (or biopsy)
# Diagnosis of PML

## PML diagnostic criteria
Consensus statement from the AAN Neuroinfectious Disease Section

![Table 2](https://example.com/table2)

<table>
<thead>
<tr>
<th>Certainty of PML diagnosis</th>
<th>Compatible clinical features</th>
<th>Compatible imaging findings</th>
<th>CSF PCR for JC virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Probable</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Possible</td>
<td>+</td>
<td>+</td>
<td>-/ND</td>
</tr>
<tr>
<td>Not PML</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Berger et al. 2013
Clinical Features

Mental status changes (personality, memory, speech)
Visual changes (hemianopia)
Hemiparesis
Seizures

**Not:** optic neuritis, spinal, fever

<table>
<thead>
<tr>
<th></th>
<th>PML (n=45)</th>
<th>RRMS (n=100)</th>
<th>P Value</th>
<th>Adjusted P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosymptomatic</td>
<td>47</td>
<td>85</td>
<td>&lt;.01</td>
<td>.02</td>
</tr>
<tr>
<td>presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>24</td>
<td>5</td>
<td>.001</td>
<td>.005</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>19</td>
<td>0</td>
<td>&lt;.0001</td>
<td>.006</td>
</tr>
<tr>
<td>Brainstem</td>
<td>2</td>
<td>18</td>
<td>.007</td>
<td>.015</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>2</td>
<td>11</td>
<td>.076</td>
<td>.076</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>0</td>
<td>33</td>
<td>&lt;.0001</td>
<td>.001</td>
</tr>
<tr>
<td>Acute spinal cord</td>
<td>0</td>
<td>18</td>
<td>&lt;.0001</td>
<td>.006</td>
</tr>
<tr>
<td>presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Boster et al, 2009
Imaging

MRI sensitive but not specific

- hyperintense on T2/FLAIR, hypointense on T1
- ill-defined borders; diffuse, multifocal
- no Gd enhancement (except in IRIS)
- no mass effect (except in IRIS)

Huang et al, 2007; Linda et al, 2009; Rahmlow et al, 2008; Carson et al, 2009
JC virus PCR in CSF:

• specificity 92-100%
• sensitivity 72-93%

only 58% in HAART (lower copy numbers?)

PCR at NIH (Major et al.) more sensitive
(8/28 patients only positive at NIH)

Clifford et al, 2010
Warnke et al, 2010
Incidence of PML in Natalizumab

<table>
<thead>
<tr>
<th></th>
<th>Worldwide</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients exposed</td>
<td>134,600</td>
<td></td>
</tr>
<tr>
<td># PML cases</td>
<td>541</td>
<td>165</td>
</tr>
</tbody>
</table>

Deaths: 23%

47 cases > 6 months follow up
13% mild disability (KS 80 - 100)
47% moderate disability (KS 50 - 70)
40% severe disability (KS 10 - 40)

Biogen, March 2015
Duration of natalizumab prior to PML 8 to 92 doses (mean 44 months)
86% had >24 doses at the time of PML diagnosis

Biogen, March 2015
Risk Perception: Patients and Physicians

- 80% of patients accept high risk
- 50% of physicians accept high risk

Heesen et al, 2010
## Risk Perception: Patients and Physicians

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Physicians</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS as malignant disease (VAS)</strong>*</td>
<td>8.5 (6.5–9.5)</td>
<td>6.5 (5.7–8.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1-year risk of walking distance &lt; 100 m°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without natalizumab</td>
<td>40% (20–50)</td>
<td>10% (0–30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>with natalizumab</td>
<td>10% (&lt;10–30)</td>
<td>&lt;10% (&lt;10–20)</td>
<td>0.062</td>
</tr>
<tr>
<td>10-year risk of becoming wheelchair-bound°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without natalizumab</td>
<td>40% (20–60)</td>
<td>30% (20–40)</td>
<td>0.081</td>
</tr>
<tr>
<td>with natalizumab</td>
<td>10% (&lt;10–30)</td>
<td>10% (&lt;10–20)</td>
<td>0.931</td>
</tr>
<tr>
<td>Patients without progression after 2 years treatment with natalizumab°</td>
<td>50% (30–70)</td>
<td>50% (30–70)</td>
<td>0.931</td>
</tr>
<tr>
<td>General natalizumab-associated PML risk (VAS)*</td>
<td>4.5 (1.7–6.0)</td>
<td>3.1 (1.8–5.0)</td>
<td>0.195</td>
</tr>
<tr>
<td>Continue natalizumab treatment (VAS)*</td>
<td>9.0 (5.1–9.5)</td>
<td>6.1 (3.7–7.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Heesen et al, 2010
Risk Factors

1. JCV antibody positivity
2. Prior immunosuppressive therapy
3. Natalizumab treatment duration
Risk Stratification

Risk Stratification Table:

<table>
<thead>
<tr>
<th>JCV Ab Status</th>
<th>No prior immunosuppressant use</th>
<th>Prior immunosuppressant use</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCV Ab negative</td>
<td>1: 10,000 patients (95% CI: 1:100.000 - 1:2,857)</td>
<td>1: 1,428 patients (95% CI: 1:2,000 – 1:1,000)</td>
</tr>
<tr>
<td>JCV Ab positive</td>
<td>≤1: 188 patients (95% CI: 1:227 – 1:162)</td>
<td>≤1: 89 patients (95% CI: 1:116 – 1:69)</td>
</tr>
</tbody>
</table>

Adapted Soelberg, Multiple Sclerosis 2012 per Biogen data 11/2013
## JCV Antibody Index

### TABLE 2. PML Risk Estimates by Index Threshold in Anti-JCV Antibody–Positive Patients with No Prior IS Use

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Index</th>
<th>PML Risk Estimates per 1,000 Anti-JCV Antibody–Positive Patients by Natalizumab Treatment Duration, No Prior IS Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–24 Months (99% CI)</td>
</tr>
<tr>
<td>≤0.9</td>
<td>0.1 (0–0.15)</td>
</tr>
<tr>
<td>≤1.1</td>
<td>0.1 (0–0.23)</td>
</tr>
<tr>
<td>≤1.3</td>
<td>0.1 (0–0.28)</td>
</tr>
<tr>
<td>≤1.5</td>
<td>0.2 (0–0.30)</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>1.2 (0.84–1.07)</td>
</tr>
<tr>
<td>No index</td>
<td>0.6 (0.42–0.88)</td>
</tr>
</tbody>
</table>

Updated per Kuesters AAN, 2015
Stratify: 2 step assay (Gorelik et al, 2010)
- ELISA with capsid protein VP1
- confirmatory ELISA (control for cross-reactivity to other polyoma viruses)

~ 60% (33-91%) of population is seropositive

2.5% false negative (some studies 35%)

5-10% seroconversion

→ need to monitor serostatus during natalizumab treatment
Does Risk Stratification Decrease the Risk of Natalizumab-Associated PML?

- JCV antibody test available since 2010
- Incidence of PML in natalizumab treated MS patients 2010-2014 unchanged

Possible reasons:
- Difficult to stop Tysabri
- Patients willing to take risk
- Sero-conversions/false negative test
- Too soon to see effect?

Cutter and Stüve, 2014
Other Potential Markers to Help in Risk Assessment

- JCV DNA in urine
- JCV DNA in blood (pathogenic genotype)
- JCV DNA in CD34 cells or B cells
- CD62L positive CD4
- Ineffective T cell responses
- Increase in JCV antibody
- JCV antibody in CSF
Clinical assessment of new neurological symptoms if suggestive of non-MS-related disease

Suspend dosing

MRI assessment

- Cannot exclude PML

PML unlikely

- Dosing may be resumed

JCV not detected and low clinical suspicion

JCV detected

- Treat as PML

JCV not detected and high clinical suspicion

- Repeat assessment
PML Treatment

• No specific treatment

• Restoring the immune system:
  antiretrovirals in HIV
  plasma exchange or immunabsoprtion of immunomodulators

• No proven benefit:
  Ara C, IFN gamma, IL-2, cidofovir, mefloquine, mirtazapine
Plasma exchange x3 (over 5-8 days)

Accelerates clearance of free natalizumab
(but still alpha-4 integrin receptor binding)

Side effects: clearance of other medications, hypotension, pulmonary edema (volume shift)
Immune Reconstitution Syndrome (IRIS)

Clinical worsening due to improvement of immune function
rapid worsening neurological symptoms, fever, seizure

In most patients with natalizumab (up to 90%)
3-6 weeks after antiretrovirals or plasma exchange

MRI:
- enlarged lesions
- contrast enhancement
- mass effect

Treatment: Corticosteroids, often requires very slow taper
Collect clinical data on PML patients entered by healthcare providers

Source of information for physicians and patients/family

https://pmlregistry.ninds.nih.gov
Easy to use online form for data entry

- secure website
- anonymized data

https://pmlregistry.ninds.nih.gov
Increase in JCV Titer

Warnke C, J Neurol Neurosurg Psychiatry 2013
JCV antibody in CSF

Warnke, von Geldern et al. 2014
Dr. Burgess Case

- 57 yo man with RRMS
- Dx’d 2003 with optic neuritis and positive MRI
- h/o copolymer
- Failed natalizumab (developed anti-natalizumab Ab)
- Dimethyl fumarate (DMF) started July 2013
Dr. Burgess Case (cont.)

- Last brain MRI January 2014 stable
- Low lymphocyte count
- Normal LFTs
- JCV +, no titer available
- LOVES being able to take a pill and not do injections
## Dr. Burgess Case (cont.) – Lymphocyte count

<table>
<thead>
<tr>
<th>Date</th>
<th>WBC K/μL</th>
<th>Lymph K/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/6/15</td>
<td>7.5</td>
<td>0.4</td>
</tr>
<tr>
<td>3/19/14</td>
<td>6.6</td>
<td>0.5</td>
</tr>
<tr>
<td>12/18/13</td>
<td>7.3</td>
<td>0.4</td>
</tr>
<tr>
<td>12/23/12</td>
<td>11.4</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Dr. Burgess Case (cont.)

Questions/Options

- Change to alternative DMT (teriflunamide or other)?
- Decrease to 240 mg q day?
- When would you consider Alemtuzumab?
- Continue as is .... If so, what safety monitoring to occur?
Dr. Kieran Case

- 61 year old female
- Diagnosed with RA 2 years ago
- Initially on MTX and then switched to adalimumab (Humira) in 2014
- RA symptoms dramatically improved
Dr. Kieran Case (cont.)

- 9 months after treatment started with adalimumab - developed saddle anesthesia that spread to all extremities
- Brain MRI - 9 enhancing lesions in the subcortical white matter
- Spine MRI - enhancing lesions in the cervical spine and conus medularis
- CSF was unremarkable (not completely done for an MS profile).
- Symptoms have almost completely resolved at this point after a course of IV and oral steroids
Dr. Kieran Case (cont.)

Questions

☐ Does she have MS?

☐ Can TNF inhibitors per se cause this?

☐ Would anyone treat with DMTs?

☐ Would further testing be helpful now or in the future if she has no further symptoms?