PML in the Biologic Era: Where We Stand

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Evidence-Based Medicine

Disclosures

- Speaker fees/advisory board
  - MSD
  - Pfizer
  - Abbott
  - GSK
- Research grant
  - Roche

Learning Objectives

- To describe the relative risk of PML associated with autoimmune rheumatic diseases
- To discuss the role of immunosuppressive therapies in the development of PML in patients with autoimmune rheumatic diseases
- To outline the approach to diagnosis and management of PML in patients with autoimmune rheumatic diseases
PML - Overview

- Progressive multifocal leukoencephalopathy
- Demyelinating CNS infection
- Rapidly fatal in most cases
- Major deficits in most survivors
- Due to reactivation of the JC virus

Polyomaviruses

- DNA viruses
  - JC, BK, (SV40)
- Almost ubiquitous
- Acquired during childhood
- Mode of transmission not clearly defined
JC Virus Infection

- Latent infection
  - Kidney, lymphoid tissue
  - CNS?
- Asymptomatic viruria
- Asymptomatic viremia
- PML - Infection of oligodendrocytes, astrocytes
- Primarily occurs in immunosuppressed pts

PML - Neuroimaging

Calabrese LH et al. Arthritis Rheum. 2007;56:2116-2128
Rapid Progression

Interval: 1 month

Koralnik IJ et al. NEJM, 2004

PML - Pathology

Confirmation of presence of JC virus by immunohistochemistry, ISH, PCR

Calabrese LH et al. Arthritis Rheum. 2007;56:2116-2128
## Underlying diagnosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>% of PML cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>80%</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>13%</td>
</tr>
<tr>
<td>Transplant recipients</td>
<td>5%</td>
</tr>
<tr>
<td>Chronic inflammatory diseases</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Series of 61 pts seen between 1996-2003

Case reports:
- Non-immunosuppressed
- HIV-negative T cell lymphopenia
- CD4 or CD8

Koralnik NEJM 2004

## Prognosis

- **No specific anti-viral Rx**
- **Non-HIV patients**
  - Median survival 2.6 months
  - 80% died by 9 months
- **HIV patients**
  - 10% 12 month survival
  - 50% with HAART
  - 80% severe neurologic sequelae
PML and rheumatic diseases

- Occasional case reports

- Assumption: related to immunosuppressive therapy

PML and the rheumatologist

- Concern re use of certain therapies
  - Rituximab
  - mycophenolate

- Evolving understanding of PML
- Differential diagnosis of neurologic manifestations of rheumatic disease
  - CNS lupus, cerebral vasculitis
PML: Rheumatologists’ Knowledge/Attitudes

- Concerns regarding PML affect both physician and patient decisions regarding the use of biologic agents
- Rheumatologists have important real and perceived learning gaps regarding PML

Calabrese LH et al Arthritis Rheum 2009 (Abst.)

Case

- 42 yo WF
- SLE x 27 yrs – Rx HCQ
- Subacute neurologic decline
- Presumed lupus cerebritis
  - Mycophenolate, steroids
  - IV cyclophosphamide, steroids
- +JC PCR in CSF
- Dx PML
- Died within 3 mo of sx onset
## PML in Rheumatic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. (%)*</th>
</tr>
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<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>32 (64)</td>
</tr>
<tr>
<td>Idiopathic inflammatory myositis (5 DM/1 PM)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Rheumatoid arthritis (1 pt with PM overlap)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Other**</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

*Through 4/09

** Sjögren’s syndrome and CD4 lymphopenia (n=1), localized scleroderma and amyloidosis (n=1) and destructive polyarthritis (+ANA, Jo1) with CD4 lymphopenia (n=1)

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## Immunosuppressive Therapy

<table>
<thead>
<tr>
<th>Treatment prior to onset of PML</th>
<th>SLE (n=32)</th>
<th>Non-SLE (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever treated with alkylators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent Immunosuppressives (&lt;6mo.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Alkylators</td>
<td>10 (31%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>- Non-alkylators +/- prednisone &gt;15mg/d</td>
<td>5 (16%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>- Low-dose prednisone +/- anti-malarials</td>
<td>10 (31%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>- None</td>
<td>1 (3%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>- Rituximab</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>- Not reported/unknown</td>
<td>6 (19%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

* No cases were reported in association with biologic therapies other than rituximab

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<table>
<thead>
<tr>
<th>PML characteristics</th>
<th>SLE</th>
<th>Non-SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ JC PCR in CSF</td>
<td>10/10 (100%)</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td>Other CSF findings:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated protein</td>
<td>1/19 (5%)</td>
<td>5/10 (50%)</td>
</tr>
<tr>
<td>Lymphocytic pleocytosis</td>
<td>0/19 (0%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Increased Immunosuppression*</td>
<td>12/24 (50%)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>Anti-viral agents</td>
<td>13/24 (54%)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>Survival</td>
<td>4/24 (17%)</td>
<td>5/13 (38%)</td>
</tr>
<tr>
<td>Interval until death, months</td>
<td>4 (3-21)</td>
<td>4 (1-6)</td>
</tr>
</tbody>
</table>

*After onset of, but prior to diagnosis of PML

Calabrese LH et al. *Arthritis Rheum.* 2007;56:2116-2128

**Conclusion**

- SLE patients may have a unique susceptibility to PML
- Not necessarily proportionate to the degree of iatrogenic immunosuppression
- Host factors clearly play a role
- Data subject to reporting bias
Nationwide Inpatient Sample

- 1998-2005 inclusive
- 297,797,180 discharges

- Confined to hospitalized patients
- Likely under-diagnosed
  – Reliant on accurate diagnostic coding
- No information regarding therapy

Molloy ES, Calabrese LH Arthritis Rheum 2009

PML – Rheumatic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>No /100,000</th>
<th>No/100,000*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>RA</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Other CTD</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>All discharges</td>
<td>3.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*After exclusion of HIV, cancer, organ transplantation

Molloy ES, Calabrese LH Arthritis Rheum 2009
Conclusions

• PML occurs rarely in patients with rheumatic diseases

• SLE associated with a predisposition to PML

JCV in SLE

• SLE (n=20)
  – No increase in asymptomatic viruria
  – Not influenced by immunosuppressive Rx
  – No patient with viremia
    • Sundsfjord et al J Infect Dis 1999

• JCV DNA not found in serum/CSF of NPSLE pts (n=71) or controls (n=58)
  • Iacobaeus et al Lupus 2013
Other Studies

• CMMS
• RA, JIA, PsA, Ps, IBD, AS
• PML=53/2,030,578
  - 2.6/100,000
• 11 without HIV/cancer
  - 0.2/100,000
• 3 biologic use
  - 1 IFX - IBD
  - 2 RTX - RA
    - Bharat et al Arthritis Care Res 2012

PML and RA

• ARTIS study
• RA 1.0 (0.3 – 2.5) n=4/66,278
• Controls 0.3 (0.1 – 0.6) n= 5/286,949
• 1 pt treated with a biologic agent
  – Arkema et al Ann Rheum Dis 2012
PML and Biologic Therapy

Natalizumab

- Binds to $\alpha_4$ integrins – interferes with normal leucocyte trafficking
- In clinical trials for RA, MS, Crohn’s
- PML: 2 MS patients, 1 Crohn’s pt
  - Berger NEJM 2005
Mechanism: 3-Step Hypothesis

- $\alpha_4$ integrins required for retention of pre-B cells and myeloid progenitors in BM
  - Increased hem. precursors in circulation $\rightarrow$ lose control of JC replication
- Decreased immune surveillance in CNS
- Suppression of trafficking of immune effectors to the CNS
  - Ransohoff Nat Neurosci 2005

Additional Cases

- 319 cases (3/2013)
  - 21.6% mortality

- REMS
- Serial MR
- Apheresis

http://www.biogenidec.com/PRESS_RELEASEDETAILS.aspx?ID=5981&RegId=1797077
## Risk Stratification

<table>
<thead>
<tr>
<th>JCV Ab status</th>
<th>Prior immuno-suppressives</th>
<th>Duration of Natalizumab</th>
<th>PML cases/ pts treated</th>
<th>PML cases/1000 pts (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEG</td>
<td>YES/NO</td>
<td>Any</td>
<td>1/11,625</td>
<td>&lt;0.09 (0 - 0.48)</td>
</tr>
<tr>
<td>POS</td>
<td>NO</td>
<td>1 – 24 mo</td>
<td>25/44,721</td>
<td>0.56 (0.36 – 0.83)</td>
</tr>
<tr>
<td>POS</td>
<td>NO</td>
<td>25 – 48 mo</td>
<td>94/20,632</td>
<td>4.6 (3.7 – 5.6)</td>
</tr>
<tr>
<td>POS</td>
<td>YES</td>
<td>1 – 24 mo</td>
<td>16/10,043</td>
<td>1.6 (0.91 – 2.6)</td>
</tr>
<tr>
<td>POS</td>
<td>YES</td>
<td>25 – 48 mo</td>
<td>52/4,681</td>
<td>11.1 (8.3 – 14.5)</td>
</tr>
</tbody>
</table>

Bloomgren et al NEJM 2012

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**Efalizumab**
Efalizumab

- 2003: FDA approved for moderate/severe plaque psoriasis
  - Not approved for PsA

- 46,000 patients treated worldwide since 2003

- 10/16/08: Black box warning re serious infections
Efalizumab and PML

• PML: 4 cases (3 fatal)
  – No prior cases reported with psoriasis
  – ~1/400 pts treated for >3 years (monotherapy)

• 2/19/09: Public Health Advisory issued by FDA
• 4/8/09: Withdrawn by Genentech
PML and Rituximab
FDA ALERT: Dec 2006

• 70 yo woman, SLE and HA
  – Rx: CTX, AZA, long term GC
  – vertigo, ataxia s/p 4 infusions of rituximab
  – + MRI and brain bx for PML, death 1 year later

• 45 yo woman, SLE x 24 yrs
  – Rx CTX IVMP, daily GC, CD4 <200
  – 2003-2005: 3 courses of rituximab with daily GC
  – April 2006: onset ‘neurologic symptoms and signs’
  – Multiple ‘brain lesions by MRI’, +JC in CSF
  – Death within 3 months


PML and Rituximab
FDA: Sept 2008

• Fatal PML dx ~ 18 mo after last dose of RTX
• Longstanding RA, Sjogren’s
• Prior Rx for RA
  – TNF antagonist prior to RTX
  – Methotrexate, steroids before, during and after RTX

• Dx oropharyngeal cancer ~ 9 mo prior to PML
  – Rx chemotherapy / radiation therapy
PML and Rituximab

- FDA Medwatch/literature
- 57 cases PML post-RTX
  - 52 lymphoproliferative disease
  - 2 SLE, 1 RA
  - 2 immune-mediated cytopenias

- 5 cases in RA
  - Clifford Arch Neurol 2011

Rituximab and PML Mechanism

- Potential pathogenic mechanism unknown
- Humoral immunity not protective
- Loss of APC function/cytokine production by B cells leads to a defect in CMI?
- Release of pre-B cells with latent JCV infection?
Boxed Warning for MMF

FDA Investigates Reports of PML in Patients Taking Mycophenolate Mofetil (MMF) and Mycophenolic Acid

“ROCKVILLE, Md (April 10, 2008) The US Food and Drug Administration is investigating a potential association between the use of mycophenolate mofetil (CellCept) and mycophenolic acid (Myfortic) -- medicines used to prevent organ rejection -- and the development of progressive multifocal leukoencephalopathy (PML), a life-threatening disease”

MMF and PML

• Jan 2008 FDA: 10 definite cases and 7 possible PML cases with MMF including 4 non-renal transplant SLE
• Retrospective cohort of 32,757 renal transplants 2000-2004
  – Incidence of PML 14/100,000 MMF vs 0/100,000 non MMF (p=NS)
• What are the risks with MMF +/- SLE??

Neff Transplantation 2008;86:1474-8
Objective

- To examine the association between PML and immunosuppressive therapies for ARD
  
  - Molloy & Calabrese Arthritis Rheum 2012

Methods

- FOI: FDA AERS database
- Nov 1, 1997 - Mar 31, 2010
- All MedWatch forms reviewed
- Further analysis if dx autoimmune rheumatic disease (ARD)
Data Collection

- **Confirmed PML**: characteristic changes on MR AND detection of JC in brain tissue or CSF
- Demographics
- Medication
- Critical clinical and lab features
- Disease association cofactors of PML

Results – Primary ARD

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Biologic Group</th>
<th>Synthetic Only Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>17</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>RA</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>34</strong></td>
<td><strong>15</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>
## Immunosuppressive Agents*

<table>
<thead>
<tr>
<th></th>
<th>Tota l</th>
<th>Biologic Group</th>
<th>Synthetic Only Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No. at onset PML</td>
<td>No.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>14</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Anti-TNF therapy</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Alkylator**</td>
<td>20</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>14</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Includes all agents associated with more than 2 cases, except glucocorticoids and anti-malarials

**Cyclophosphamide in all cases except for 2 cases in SO group treated with chlorambucil

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## Rituximab

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of courses</td>
<td>2</td>
<td>1-4</td>
</tr>
<tr>
<td>Interval since 1(^{st}) infusion (mo)</td>
<td>12</td>
<td>1-57</td>
</tr>
<tr>
<td>Interval since last infusion (mo)</td>
<td>5</td>
<td>0-29</td>
</tr>
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</table>

Molloy & Calabrese Arthritis Rheum 2012
### Rituximab – Potential Confounders

<table>
<thead>
<tr>
<th>Confounder</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Lymphopenia</td>
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<tr>
<td>Cyclophosphamide - Past</td>
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<tr>
<td>- Present</td>
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<tr>
<td>Current Immunosuppressives - Methotrexate</td>
<td>X</td>
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<td>X</td>
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<td>X</td>
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<td>- Mycophenolate</td>
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<td>- Azathioprine</td>
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<tr>
<td>- Leflunomide</td>
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<td>Malignancy - Chemotherapy</td>
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<tr>
<td>- Radiotherapy</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

No patient with HIV, organ transplantation  

Molloy & Calabrese Arthritis Rheum 2012

### PML and Rituximab

**Published Literature**

- **RA 5**
- **SLE 2**
- **Polymyositis 1**
  - Harris Rheumatology 2008
  - Fleischmann Arthritis Rheum 2009
  - Carson et al Blood 2009
  - Clifford et al Arch Neurol 2011

- **7 additional cases in the current study**
Anti-TNF therapy
Confirmed PML cases

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Dx</th>
<th>Agent</th>
<th>At onset PML?</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>73F</td>
<td>RA, Sjogrens</td>
<td>Etanercept</td>
<td>No</td>
<td>4 courses RTX after anti-TNF Concomitant MTX, pred Chronic lymphopenia</td>
</tr>
<tr>
<td>51F</td>
<td>RA, Sjogren's</td>
<td>Infliximab</td>
<td>No</td>
<td>RTX after anti-TNF, lymphopenia Also MTX, HCQ SCC oropharynx → chemo, radiotherapy</td>
</tr>
<tr>
<td>55F</td>
<td>RA</td>
<td>?</td>
<td>No</td>
<td>3 courses RTX after anti-TNF</td>
</tr>
<tr>
<td>62F</td>
<td>RA</td>
<td>Etanercept</td>
<td>No</td>
<td>3 courses RTX after anti-TNF Chronic lymphopenia</td>
</tr>
<tr>
<td>42F</td>
<td>Dermatomyositis</td>
<td>Infliximab</td>
<td>No</td>
<td>1 course RTX after anti-TNF Onset 3 mo after last infliximab</td>
</tr>
<tr>
<td>69M</td>
<td>RA vasculitis</td>
<td>Infliximab</td>
<td>Yes</td>
<td>Concomitant CYC, HCQ, pred.</td>
</tr>
</tbody>
</table>

Median interval from D/C anti-TNF 3 yrs (range 3mo – 5yrs)

Other Biologic Therapies

- No confirmed PML cases a/w use of other biologic therapies for rheumatic disease e.g. tocilizumab or abatacept
- One case had exposure to anakinra 2y prior to onset of PML
Limitations

- Reporting bias (voluntary)
- Variable completeness of reports
- Small numbers of PML cases
- Inability to derive a true numerator or denominator

Conclusions - Rituximab

- Concerning signal emerging
- Very rare (i.e. <1/10,000)
  - RA: 6/209,000 (May 2012)
- Other ARD: 10/??
- Ongoing vigilance required
  - Esp if exposed to alkylator, ?SLE
- Mechanism of increased risk?
Conclusions – anti-TNF therapy

• Paucity of unconfounded confirmed cases in patients treated with anti-TNF
• Denominator estimate ≥3 million pts
• Little evidence of a clearcut risk of PML

Case Reports – Confirmed PML

• Infliximab
  • RA – MTX, IFX
    • Kumar et al Arthritis Rheum 2010
  • PAN, MDS - prior CYC, others
  • 2 cases immunodeficiency
    • Meyts et al Bone Marrow Transplant 2009
    • Moshous et al J All Clin Immunol 2011

• Adalimumab
  • GPA – CYC+adalimumab x 4 y

• Etanercept
  • SLE, erosive polyarthritis – pred, ETA
    • Graff-Radford Neurologist 2012
Conclusions - Mycophenolate

- 6 cases
  - Prior CYC in all 6
  - 5 with SLE
  - MMF ongoing at dx PML in 4 cases

- No clear signal above that seen with other non-biologic agents e.g. azathioprine, cyclophosphamide

Belatacept

- Recombinant soluble fusion protein
  - extracellular domain of human CTLA-4
  - fragment of a modified Fc domain of IgG1
- 2nd generation, higher avidity version of abatacept, differ by only 2 amino acids
- Mar 2010
  - FDA advisory ctee approval for prophylaxis of renal transplantation
Belatacept and PML

• Renal transplantation
  – 1/949 pts PML
  – More intensive regimen, MMF, CS x 2 y
  – 63 WF, fatal + JC by CSF PCR

• Liver transplantation
  – Belatacept, MMF, CS x 6 mo
  – 52 WM, + JC by CSF PCR
  – D/c Belatacept, MMF
Conclusion

• PML is a reported complication of:
  – Various ARD
  – synthetic and biologic immunosuppressive therapies

• All patients treated with immunosuppressive therapies for rheumatic disease should be considered potentially at risk for PML

Practical Points

• Can I predict PML risk?

• How do I recognize PML?

• What can I do about it?
Risk Predictors?

- SLE
- HIV/organ transplantation
- Sustained lymphopenia
- JCV ab status?

JCV Ab testing

- JCV Ab - 37% false negative rate
- 75% of pts infected
  - Berger et al Ann Neurol 2013

- Titer rises at/prior to dx of PML?
  - Warnke et al JNNP 2013

- Other biologics - no currently defined role
Clinical Suspicion

- Consider PML in patients with unexplained progressive neurologic deficits with subacute onset
- Especially if worsening/not-responsive to immunosuppressive therapy
- Spinal cord/optic nerve involvement argue against PML

Diagnosis

- Normal MRI has high negative predictive value but normal LP does not
  - Frank infarction not a feature of PML
  - Contrast enhancement may occur in PML

- **JC virus PCR** in CSF is critical for early diagnosis - may need to be repeated

- **CNS Biopsy** indicated for atypical cases, PCR-neg, deteriorating on IS therapy
Management Approach

• Potentially better outcomes if:
  – High index of suspicion maintained
  – Early diagnosis
  – Prompt withdrawal of immunosuppressive Rx

• Rule out HIV

• No proven drug therapy
  – Apheresis – natalizumab only

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