PML and IRIS

Complication under Monoclonal Antibody Therapy

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No conflicts of interest

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Outline

**What are we talking about?**
Therapy of MS and side effects
What is PML and IRIS?

**What is the contribution of neuroimaging?**
Characteristic brain lesions others than MS

**Implications for patient care**
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Implications for patient care
Recombinant monoclonal antibody (Natalizumab)

Mode of action:

- Inhibitor of selective adhesion molecule (VLA-4)
- Reduction of cerebral inflammatory reactions

Reduction of relapses (68%)

Reduction of Gd+ enhancing lesions (90%)

Reduction of handicap progression (54%)

Tysabri® prescribing information. Biogen Idec Inc.
What is PML* and IRIS?

**Progressive Multifocal Leucencephalopathy***

Opportunistic CNS Infection

Human Polyoma Virus (1971)  
J.C.-Virus (Index Patient)

Lytic infection of oligodendrocytes

124 confirmed cases (May 2011)  
under therapy with Natalizumab

Cognitive and personality changes, visual or motor symptoms and seizures

Falco et al. 2008; JAIDS 49: 26-31
Recombinant monoclonal antibody (Natalizumab)

Individual Risk:

- 70-85% of population positive for JC Virus

- Increased risk with prior immunosuppression

0.01/1000 during months 1-12

0.39/1000 during months 13-24

1.46/1000 during months 25-36

Vermersch et al. 2011; Neurology 76:1697-1704

Sandrock et al. 2011; AAN P03.248 - Risk Stratification for PML on Natalizumab
What is PML and IRIS**?

**Immune Reconstitution Inflammatory Syndrome**

Paradoxic deterioration of clinical response due to worsening of PML symptoms after plasma exchange therapy

May occur spontaneously after withdrawal of Natalizumab

Hypercellular gray and white matter with gliosis

Moderate perivascular inflammation

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Demyelinating Lesions

**MS:** Multiphasic, smaller (<1.5 cm) WM lesions, cortex and spinal chord may be involved

**PML:** Progressive, patchy WML, may enhance in MS-PML, U-fibers

**ADEM:** Monophasic, larger (1-2 cm) WM lesions, deep WM, confluent spinal lesions, BG & thalamic

**PRES:** Patchy, confluent lesions, cortical/subcortical, asymmetric, variable enhancement

**HIV:** Atrophy, symmetric periventricular or diffuse WM, nonenhancing
PML:

Scalloped appearance

Subcortical - deeper white matter - centrum semiovale - periventricular regions

1, 2: Courtesy of EW Radue, with permission
Imaging findings

**PML:**

Scalloped appearance

Subcortical - deeper white matter - centrum semiovale - periventricular regions

Confluent – bilateral - asymmetric supratentorial - white matter

1, 2: Courtesy of EW Radue, with permission
Imaging findings

**PML:**

- Scalloped appearance
- Subcortical - deeper white matter - centrum semiovale - periventricular regions
- Confluent – bilateral - asymmetric supratentorial - white matter
- Parietal lobe - frontal lobe
- Middle cerebellar peduncle – pons – cerebellum
- Spinal chord (very rare)
Imaging findings

**PML:**

- T2 / FLAIR hyperintense
- T1 iso- to hypointense
- U-Fibers involved
- May enhance in MS-PML (usually not in HIV-PML)

Courtesy of EW Radue, with permission
Imaging findings

IRIS:

Development of enlarging MRI lesions on T2w

New or increased gadolinium enhancement on MRI scans

No definite way to differentiate IRIS from PML progression

High ADC values within PML lesions before immune reconstitution may be a risk factor for IRIS (ADC ratio>2.2)

Buckle & Castillo. 2010; AJNR 31:1031–35

Schröder et al. 2008; Arch Neurol 67: 1307-11
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Implications for patient care
MRI + Gd ahead of therapy (within 3 months)

MRI + Gd follow up every year (compare with baseline)

MRI + Gd immediately - whenever new symptoms are not explained by MS (think of PML)

Consider IRIS after immune reconstitution (withdrawal of Natalizumab / plasma exchange)