Immune Reconstitution Inflammatory Syndrome

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IRIS Definition

- There is no widely accepted standard definition of IRIS
- “Paradoxical deterioration in clinical status attributable to recovery of the immune system”[1]
- First recognized with HIV infection after the introduction of highly active antiretroviral therapy
  - ↓HIV load → ↑CD4 (and CD8)[2] → recovery of T cell specific immune response
  - 90% ↓HIV within 2 weeks of HAART
  - IRIS develops with 2-3 months of HAART (1-104 weeks)

1. Shelburne SA et al: Medicine 2002;81:213-27. 2. DeSimone JA et al: Ann Intern Med 2000;133:447-454.

Categories of IRIS in HIV Infection

Table I. Categories of immune reconstitution inflammatory syndrome

Category	Antigen target	Examples
Infectious – unmasking	Viable replicating infective antigen	Unmasking of cryptococcal meningitis
Infectious – paradoxical	Dead or dying organism (patient on appropriate treatment for infection)	Tuberculosis paradoxical reaction
Autoimmune	Host	Graves' disease (thyroid)
Malignancies	Possible tumour or associated pathogen	Worsening of Kaposi's sarcoma
Other inflammatory conditions	Range	Inflammation at site of tattoo; sarcoidosis

- Conditions reported with IRIS in HIV[2]
  - MAI, M. Tb, B. henselae, C. neoformans, PCP, CMV, HSV, VZV, Hepatitis C, Hepatitis B, PML
  - Kaposis sarcoma, sarcoidosis, Graves disease
- Increased risk with greater severity of illness[3]
- PML-IRIS may occur in up to 23% of HIV-associated PML[4]
- Survival in HIV-associated PML unaffected by IRIS

1. Dhasmana DJ et al: Drugs 2008;68:191-208. 2. Shelburne SA et al: Medicine 2002;81:213-27. 3. Robertson J, et al: Clin Infect Dis 2006;42:1639-46. 4. Cinque P et al: Lancet Infect Dis 2009;9:625-36.

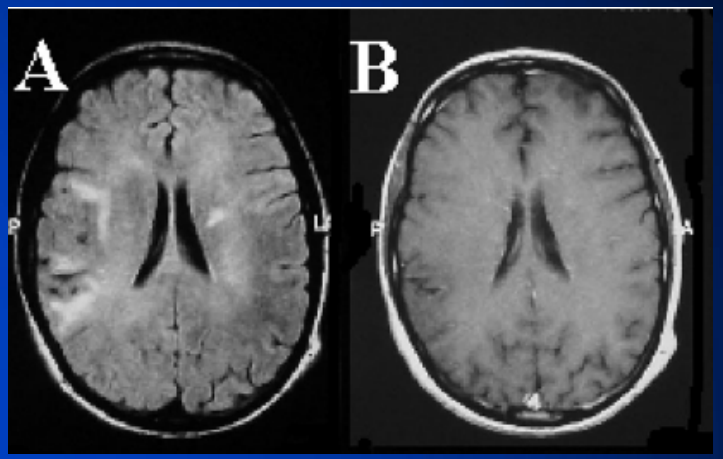
Pathogenesis of IRIS

- The pathogenesis of IRIS is poorly understood.
  - Reconstitution of the immune cell numbers and function
  - Redistribution of lymphocytes
  - Defects in regulatory function
  - Changes in Th_1 v Th_2 profile
  - Genetic susceptibility
  - Antigenic load
- Accounts for clinical and pathological heterogeneity

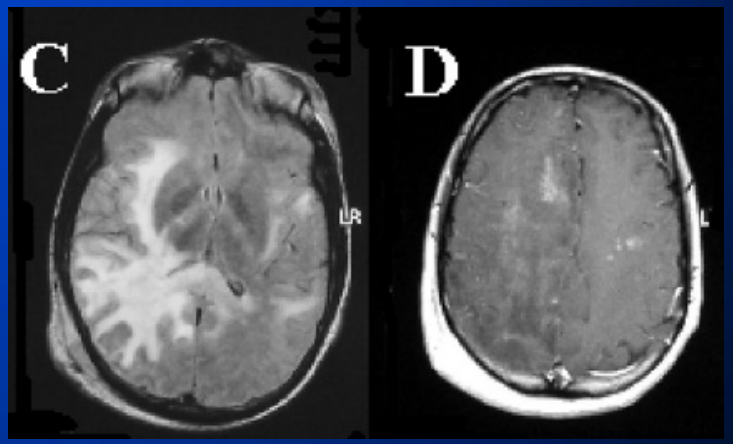
Dhasmana DJ et al: Drugs 2008;68:191-208.

Features of PML IRIS in HIV

- Clinical worsening
- MRI progression
  - Extension of lesion on T2WI and FLAIR
  - Contrast enhancement (may be transient)
  - Brain edema



Initial MRI July 2004



Follow-up MRI Oct 2004

Martinez JV et al: Neurology 2006; 67:1692-4

PML-IRIS with Natalizumab Representative Case

- 21 year old woman
- RRMS x 15 years
- PML after 29 months of natalizumab
- Heralded by seizures
- Rx with PLEX, mirtazapine and mefloquine
- Worsening 1 week after PLEX
- IVMP 500 mg/d x 5 d and mannitol

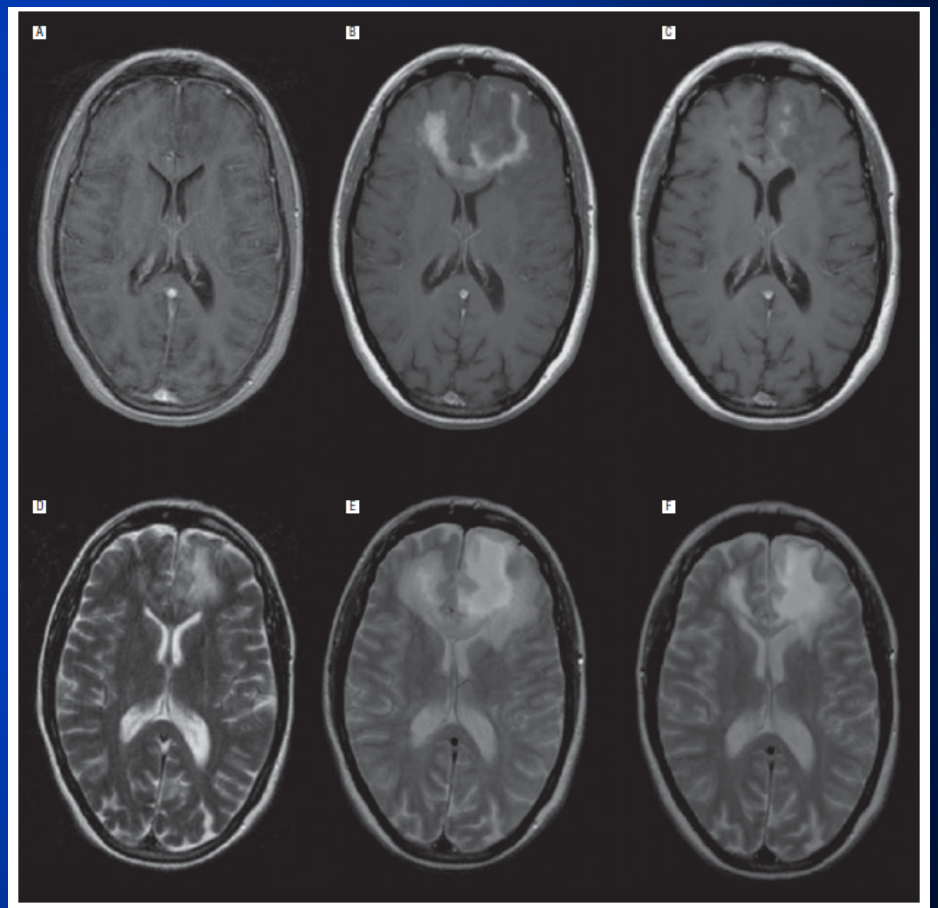
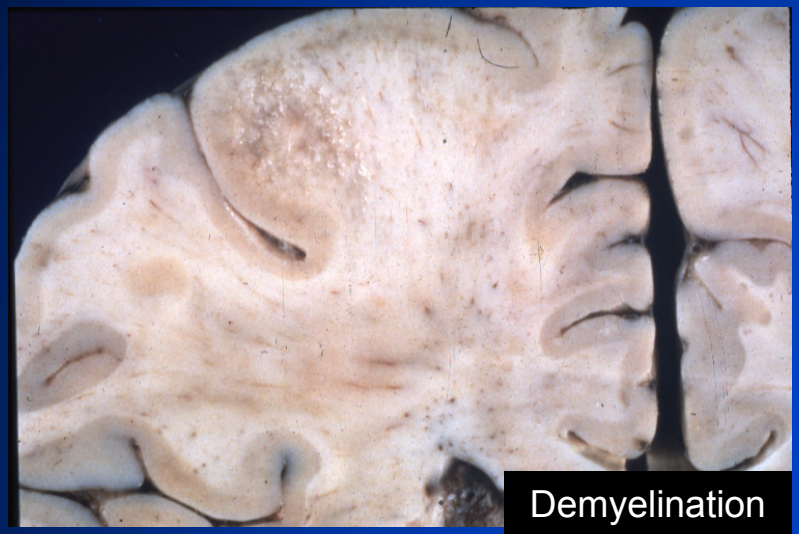
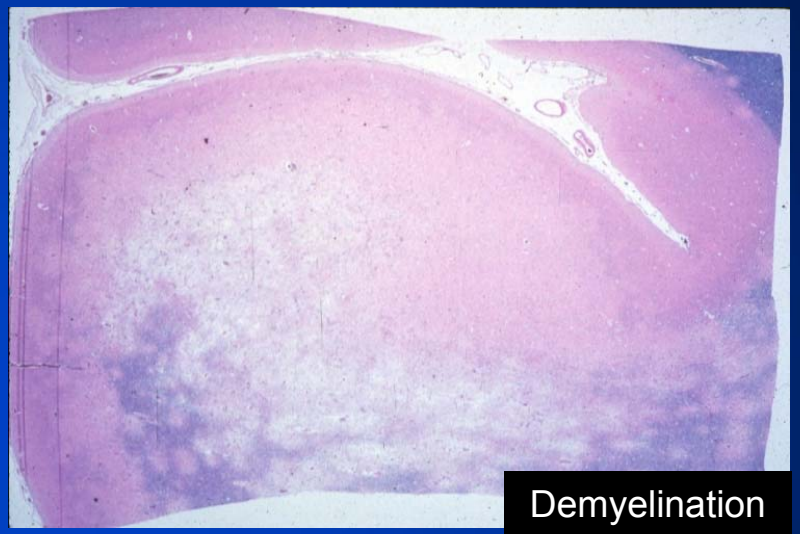


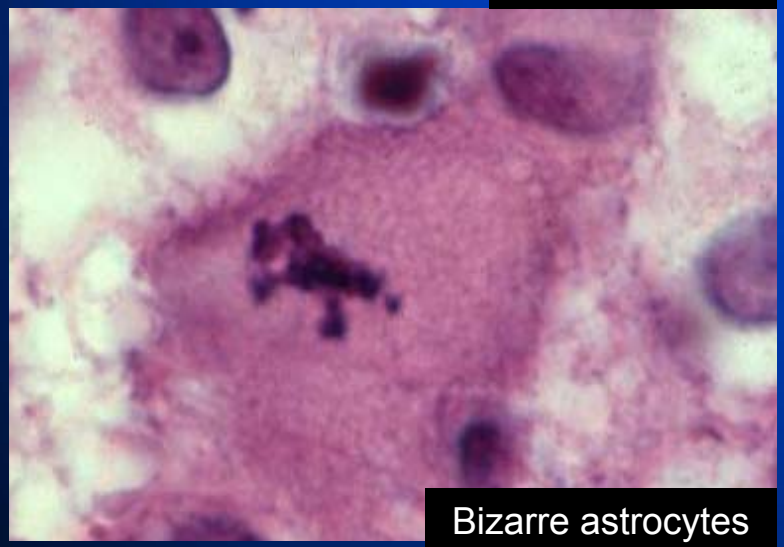
Figure. Serial axial postcontrast T1-weighted (A-C) and T2-weighted (D-F) magnetic resonance images of the brain at the point of progressive multifocal leukoencephalopathy diagnosis (A and D), in the immune reconstitution syndrome phase (B and E), and after treatment (C and F).

Schrôder A et al: Arch Neurol 010;67:1391-4.

Pathology of PML


Demyelination


Demyelination


Bizarre astrocytes


Enlarged oligodendroglial nuclei

Pathology of PML-IRIS

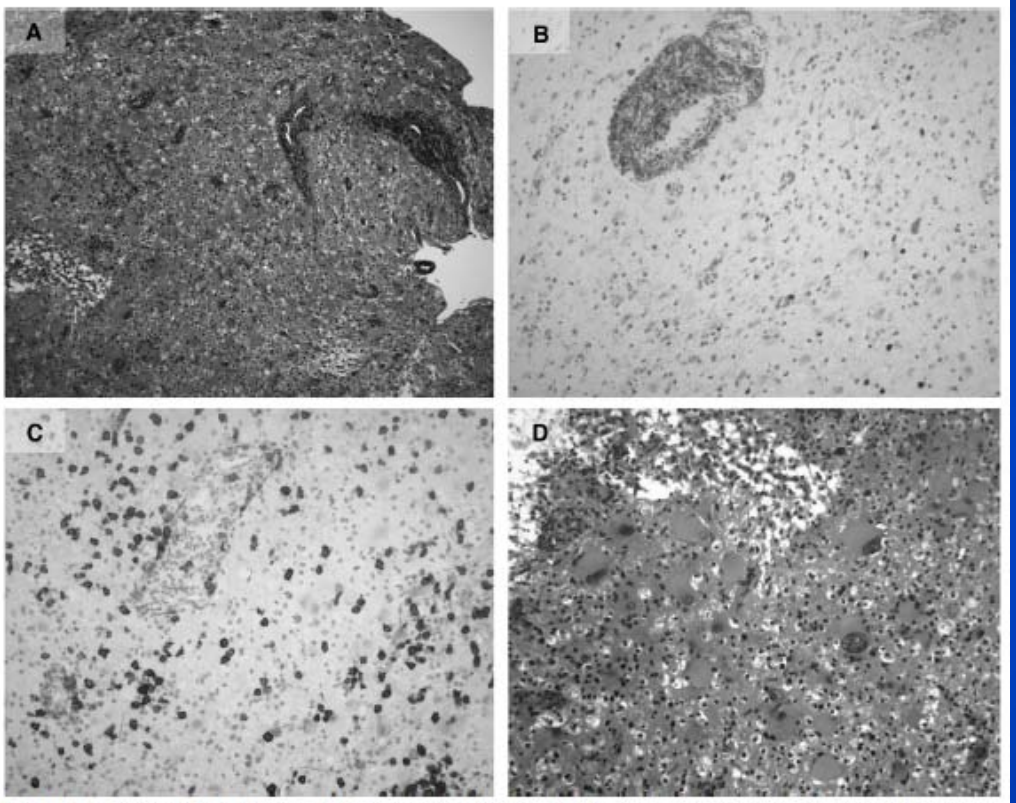
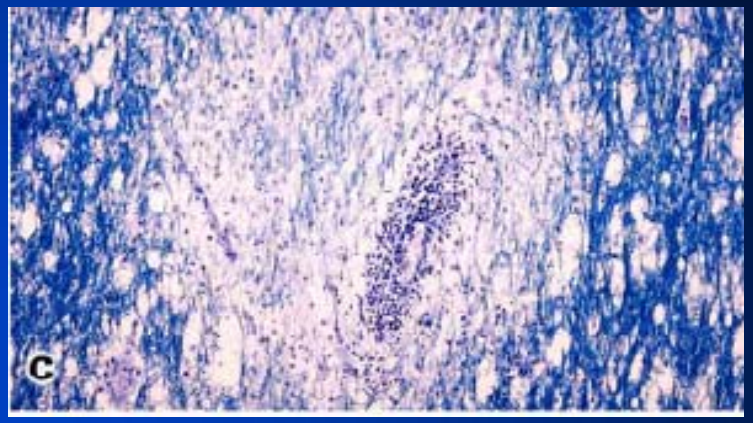
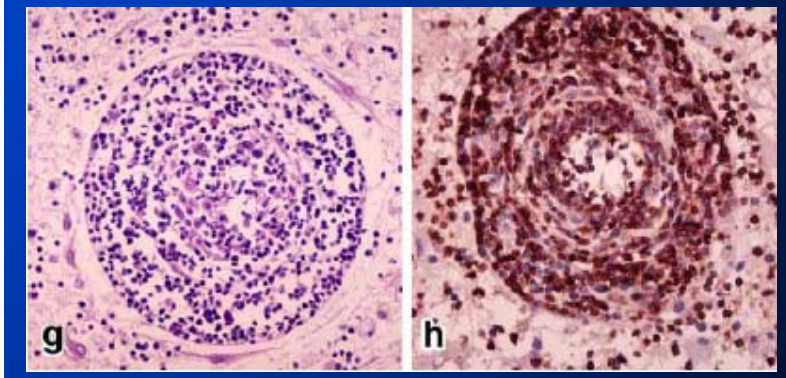


FIGURE 2. A, Subcortical white matter showing prominent inflammation, demyelinating phagocytic activity, and perivascular lymphocytic cuffing (H&E, original magnification ×100). B, $CD4^+$ T-lymphocytes showing a mainly perivascular distribution in the white matter with some parenchymal infiltration as well (CD4 immunostaining, original magnification ×200). C, Prominent plasmacytic contribution to the leukoencephalitic process with a mainly parenchymal distribution (CD138 immunostaining, original magnification ×200). D, Bizarre astrocytosis against a background of confluent demyelinating phagocytic activity (H&E, original magnification ×200).



Acute perivenular demyelination and inflammation



Intense perivascular inflammation with CD8+ cells

Travis J et al: PML IRIS Neurologist 2008;14:321-6

Vendrely A et al: Acta Neuropath 2005; 109:449-55.

Treatment of PML-IRIS in HIV Infection

- Common therapeutic intervention is high dose corticosteroids
  - Typically dramatic clinical improvement
  - No increase in adverse events[1]
  - Trend but no statistically significant difference in survival with steroid treatment of PML-IRIS in HIV[2]
    - Early corticosteroid introduction
    - High doses
    - Prolonged administration

1. McComsey GA et al: AIDS 2001;15:321-7. 2. Tan K et al: Neurology 2009;72:1458-64.

PML-IRIS with Natalizumab

- Review of 28 confirmed natalizumab-associated PML between July 2006-November 2009[1]
- IRIS occurred in almost all cases
- Characterized by
  - Subacute progression and exacerbation of earlier symptoms
  - Enlarging MRI lesions or contrast enhancement
- IRIS occurred even in absence of PLEX
- Mortality 28.5% (8/28)
- JCV may persist in CSF even months after IRIS[2]

1. Clifford DB et al: Lancet Neurol 2010;9:438-46. 2. Ryschkewitsch MT et al: Ann Neurol 2010;68:384-91.

Tysabri-treated PML Cases

Frequency of IRIS is Similar in Patients With or Without PLEX/IA

- As of 28-Jan-2011 with 93 confirmed PML cases, the majority of patients (84/93, 90%) underwent accelerated removal of Tysabri from the circulation by PLEX and/or IA

Treatment Received (PLEX and/or IA)	Number of Confirmed PML patients (N=93)	Number/percent of patients who developed IRIS
PLEX alone	76	56/84 (67%)*
IA alone	4	
PLEX and IA	4	
NO PLEX or IA	4	4/4 (100%)
Unknown status	5	4/5 (80%)

84 patients

* 2 patients (2/84, 2%) did not develop IRIS and the occurrence of IRIS was either not reported or unknown for 26 patients (26/84, 31%)

- IRIS usually occurred days to several weeks after PLEX/IA
- Without PLEX/IA, IRIS usually occurred ~3 months after the last dose of Tysabri
- Most patients were treated with corticosteroids for IRIS (or IRIS prophylaxis) 73/93, 78%; 7 patients were not treated with corticosteroids and it was unknown if corticosteroids were prescribed in 13 patients.

BiogenIdec communication July 22, 2011

Recommended Treatment for PML-IRIS

- No controlled trials to date
- Suggested therapies
  - 1 g IVMP for 3-5 days followed by oral taper over 6-8 weeks[1]
  - 1 g IVMP for 5 days followed by oral taper over 2 weeks[2]
    - If symptoms during or after taper worsen, re-treatment with the same dose or IVMP 2 g for 5 days with subsequent taper

1. Johnson T and Nath A: Curr Opin Neurol 2011;24:284-90. 2. Hartung H-P, Berger JR, et al: Actuelle Neurologie 2011;38:2-11.

Medicine is a science of uncertainty and an art of probability.

Sir William Osler
1849-1919