Immune Reconstitution Inflammatory Syndrome

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Immune Reconstitution Inflammatory Syndrome (IRIS)

• Definition
• Clinical settings
• Pathology
• Diagnosing IRIS in MS patients treated with Natalizumab
• Treatment
Immune Reconstitution Inflammatory Syndrome (IRIS)

- French et al 1992 noted restoration of DTH within 6 months in 42% of a series of initially anergic individuals with HIV started on Zidovudine.
- In 4/9 with a maximal DTH response (≥8mm), and one additional individual who developed a positive MAI PPD, an acute febrile illness developed within two weeks associated with localized MAI infection.
- They proposed that the restoration of immunity resulted in an acute inflammatory response to MAI antigens in tissues previously colonized.

Defining IRIS

- Shelburne et al proposed the term Immune Reconstitution Inflammatory Syndrome (IRIS) to represent a process in which clinical deterioration occurs shortly after initiation of HAART due to restoration of the capacity to mount an inflammatory immune response to either infectious or non-infectious antigens.
- They noted that in some cases the infectious agent was known to be present and under treatment prior to HAART initiation while in others, the infection was indolent but became apparent only after the inflammatory response developed.
- They reported a case in which Grave’s disease developed following HAART in the absence of any new infection (and reviewed similar cases reported by others) suggesting that an auto-antigen could also incite the inflammatory response.
Two Types of IRIS

• Paradoxical /Delayed
  – Occurs in an individual following treatment and stabilization of a known infection at the time of immune reconstitution
  – Following initiation of HAART (typically w/in weeks to months) the infection appears to worsen in association with restoration of CD4+ T-lymphocyte counts, and reduction in HIV RNA plasma load
  – Histopathology demonstrates a vigorous inflammatory response in affected tissues in the absence of active infection
• In non-HIV-infected individuals, restoration of immune function can produce a similar pattern


Two Types of IRIS

• Unmasking /Simultaneous
  – Initiation of HAART is associated with the emergence of a previously occult infection, usually within the first weeks of therapy
  – Viable pathogens are isolated
  – Inflammatory reaction is directed at the active infectious agents
• A similar pattern can be seen in non-HIV infected individuals with reversal of immune suppression

IRIS Risk Factors

- Intensity of immune suppression
  - nadir CD4+ prior to HAART (<50-100 cells /mm3)
- Rate / Degree of Reconstitution
  - Plasma HIV RNA decrease > 1 to 2.5 log within 3 months of HAART
  - PBMC IL-6 levels increased in patients developing IRIS
- High pathogenic antigen burden
- ? Host genetic factors influencing immune response or pathogen clearance


IRIS in Non-HIV infected populations

- Transplant populations following withdrawal of immune suppressive treatment and initiation of antimicrobial therapy for an active infection
- Individuals with tuberculosis or leprosy following initiation of antimicrobial therapy
- Rapid recovery from induced neutropenia
- Women in the post partum period
- Individuals with autoimmune disorders; in association with immune suppressive therapy, due either to infectious or non-infectious antigens

Singh N, Perfect JR. Clin Infect Dis 2007;45:1192-1199
IRIS in non-HIV with Immune Therapy

• Tumor Necrosis Factor Antagonists
  – TNF can activate macrophages, recruit immune cells, enhance granuloma formation
  – Risk of tuberculosis increased in patient taking TNF-α antagonists
  – Discontinuation of TNF-α antagonists in patients treated for emergent TB associated with subsequent IRIS 1-16 weeks later


IRIS after Natalizumab Cessation?

• Rebound MS activity following discontinuation of natalizumab therapy
  – Series of 32 patients without PML
  – 38% RRMS, 25% SPMS patients relapsed
  – Marked inflammatory activity on MRI in excess of that seen in patients prior to starting natalizumab therapy
  – Diffuse inflammatory activity considered similar to that seen in PML-IRIS
  – MS activity suppressed by resumption of natalizumab therapy

• Case report: severe relapse 9 weeks after discontinuation of natalizumab for intended pursuit of pregnancy.
  – Failure of response to multiple IVMP pulses led to PLEX followed by further worsening with multiple enhancing lesions.
  – CSF negative for JCV on 3 samples.
  – Biopsy revealed inflammatory demyelinating lesions, no PML.
  – Patient reported to have ARR of 3-4 prior to starting natalizumab

Miravalle A. Arch Neurol 2011;68:186-191
Lenhard T et al. Neurology 2010;75:831-833
Natalizumab - associated PML IRIS

- Retrospective review of 42 cases reported to Medwatch,
  - Classified by early enhancement at diagnosis of PML or later appearance of enhancing lesions.
  - Contrast enhancement in 17/42 at PML diagnosis prior to withdrawal of NTZ (early IRIS), 23 after PML diagnosis and withdrawal of NTZ and PLEX (late IRIS)
  - Mean duration from PLEX to IRIS 2.8 wks in early IRIS compared to 4.3 weeks in late IRIS
  - Following PLEX / IA; CSF JCV load increased in those enhancing at presentation (4/9 paired samples) by >10x but <2x in those enhancing following PLEX /IA (5/9 paired samples)

Tan IL et al Neurology 2011;77:1061-1067

Natalizumab - associated PML IRIS

- No correlation between initial CSF JCV Viral load, or prior immune suppressive therapy, and mortality
- No difference in mortality between early and late IRIS
- In those with enhancement prior to PLEX / IA, disability outcome trended worse with mean f/u EDSS 8.7 vs 7.1 (p>0.05)
- Corticosteroid therapy during IRIS associated with more favorable disability outcomes

Tan IL et al Neurology 2011;77:1061-1067
Pathogenesis: HIV IRIS

- Immune pathogenesis still incompletely understood
- IRIS typically appears within 3-6 months of HAART initiation but can appear later
- Chronic IRIS reported up to years following immune reconstitution
- CD4+ T cells which appear in the first few weeks following initiation of HAART are effector memory cells released from lymphoid tissues.
- CD8+ T effector memory cells also increase in first two months but are replaced by naïve CD8+ within months on HAART
- Believed that pathogenic T cell response in IRIS is derived from memory T cell pool
- Subsequent increases in CD4+ and CD8+ lymphocytes resulting from proliferation of naïve T cells can continue for years
- CNS IRIS occurs in about 1%

Martin-Blondel G. Brain 2011;134:928-946

Pathogenesis: HIV-IRIS

- IRIS pathology may vary with triggering pathogen / antigen
- CD8+ T cell infiltration: PML, HIV, Herpes viruses, Toxoplasmosis
- CD4+ Th1 T cells implicated in mycobacterial and cryptococcal granulomatous IRIS
  - Cryptococcal IRIS associated with higher CSF CXCR3+ CCR5+ CD8+ T cells
  - Higher Pre – ART serum levels of IL4 and IL17, and lower TNFα, GCSF, GMCSF, and VEGF predicted cryptococcal IRIS. Post - ART; increased CRP associated with shorter time to IRIS
  - TBM-IRIS associated with higher CSF neutrophils, TNF-α, lower IFN-γ
- Lymphopenia induced homeostatic proliferation:
  - Ag driven, influenced by T cell Receptor affinity;
  - Early immune restoration might bias to proliferation of memory effector cells
- Autoimmune Antigens
  - Lymphopenia / Homeostatic proliferation may predispose to autoimmune disorders with immune restoration due to epitope spreading or molecular mimicry
  - Inflammatory response directed at a self antigen difficult to distinguish from one directed at a persisting pathogenic antigen, both may occur

HIV-IRIS: Pathogenesis

- HAART-induced IRIS patients may have elevated serum levels of proinflammatory cytokines (IFN-γ, IL-6) and inflammatory markers (eg; CRP) suggesting chronic immune activation
- Tregs in IRIS patients do not differ in frequency, but could be functionally impaired
- Recent Hypothesis: Imbalanced activation of the innate immune system through activation of pattern recognition receptors in macrophages, in the absence of CD4+ cells, could result in primed macrophages, which then respond exuberantly to CD4+ T lymphocyte restoration and second signaling
- Genetic Susceptibility via polymorphisms in immune response genes; eg: HLA A2, B44, DR-4, IL12, IL-6, TNF-α

Natalizumab associated PML IRIS

- Pathology:
  - CD8+ T cell infiltrate in both demyelinated lesions and non-demyelinated white and adjacent gray matter
  - CD8+ T cells = 8x control PML cases
  - Similar to HIV associated PML-IRIS
  - Plasma cells in lesions, and in non-demyelinated white and adjacent gray matter; 125x greater than in MS plaques
  - CD8+ T, CD4+ T, & CD19+ B cells in perivascular spaces
  - Activated Macrophages
  - Chronic cavitary lesions
CD8+ T cell inflammation in Natalizumab associated PML-IRIS

Histology of IRIS is characterized by extensive T-cell inflammation in natalizumab-associated PML. An inflammatory demyelinating lesion with pronounced inflammation is shown (a H&E, b LFB/PAS). T cells are dominated by CD8+ T cells (c CD3, d CD8). Inflammation is also evident in adjacent nondemyelinated white and grey matter (e + f CD3). Original magnifications: a + b x40; c-f x 100. Scale bars 200 μm.


Plasma Cells in MS-Natalizumab associated PML-IRIS

High numbers of plasma cells are evident in natalizumab associated PML with IRIS.

Strikingly high numbers of plasma cells are found in MS–PML–IRIS lesions (a).

Lower numbers are present in inflammatory PML cases (b).

In MS–PML–IRIS, plasma cells are also evident in non-demyelinated white and grey matter (c, d)

(a–d CD138). Original magnifications: a–d x 100. Scale bars 200 μm.

a + d Patient 2, b inflammatory PML control, c patient 1

Cavitary lesions in chronic Natalizumab-associated PML-IRIS


Natalizumab associated PML-IRIS: CD4+ T lymphocytes

- Brain biopsy in patient with low CSF JCV VL and high titer IgG1 and IgG3 antibodies to VP1
  - Massive perivascular and parenchymal lymphomononuclear infiltrate
  - Majority of cells were HLA DR+
  - T cell infiltrate contained 70% CD4+ and 24% CD8+; virtually all were CD45+RO+ memory cells
  - 29% CD19+ B cells; 86% were CD27/CD38+ memory B/plasma cells
  - Immunohistochemistry for JCV was negative, sparse in situ hybridization signals
- Ex vivo T cell cultures and CD4+ T cell clones were established
  - Brain derived CD4+ T cells were highly proliferative in response to VP1 peptides in contrast to those from CSF
  - CD4+ T cells: Th1= 46-53%, in brain and CSF
  - 32.7% Brain derived CD4+ were bifunctional Th1-2 secreting both IFNγ & IL-4
  - Found also in controls with PML, but not non-PML controls
  - Brain derived CD4+ T cells demonstrated JCV specific VP-1 response which was HLA restricted by DRB*15:01/BS*01:01.
  - VP1 contains epitopes recognized by both JCV specific CD4+ and CD8+ T cells

Aly L. Brain 2011;134:2687-2702
Natalizumab associated PML IRIS
CD4+ T lymphocytes

• Hypothesized:
  – Th1-2 phenotype which secretes both IFNγ and IL-4 induces the expression of MHC II on resident microglia, macrophages & infiltrating immune cells
  – JCV specific Th1-2 and Th1 lymphocytes reactivated in CNS by recognition of JCV peptides on HLA-MHC-II+ APCs
  – IL-4 activates memory B cells and plasma cells to produce antibodies to VP1; recognizing JCV-infected oligodendrocytes, which might then be lysed by C' dependent or Ab dependent cellular cytotoxicity
  – JCV specific CD8+ T cells also have a role recognizing MHC I bound antigen on infected oligodendrocytes and astrocytes
  – Strength of the immune response (IRIS) may be in part determined by HLA type

Aly L. Brain 2011;134:2687-2702

Persistent Natalizumab PML IRIS

• Case report of PML symptomatic with IRIS, but retrospectively present on MRI 3 months prior
  – Two courses IVMP produced clinical improvement
  – Worsening w/o new symptoms on MRI two months later
  – Regression 7 months after treatment / 11 months after retrospective appearance on MRI
• Autopsy case describing active PML-IRIS lesions nine months following IRIS presentation (1 year from 1st symptoms PML)
  – Progressive deteriorating course despite steroids, mirtazapine and mefloquine
  – Few or no JCV infected cells
  – No active MS lesions
  – Foci of persistent IRIS
  – Cavitary lesions
  – Microglial clusters and activation in adjacent gray matter

Natalizumab associated JCV Granule Cell Neuronopathy IRIS

- Presentation with progressive cerebellar symptoms evolving over 5 months
- MRI showed cerebellar atrophy evolving over 7 month interval without T2 lesions or contrast enhancement
- CSF detection JCV DNA
- Stabilized then worsened two months following PLEX, (3 months following Natalizumab discontinuation)
- Cerebellar biopsy demonstrated loss of GCN, few JCV infected cells and inflammatory infiltration consistent with IRIS; restricted to granular cell layer
- Clinically stabilized with persistent cerebellar deficits at 17 months post onset


Diagnosis of IRIS in MS patients with Natalizumab associated PML

- The challenge is distinguishing worsening PML vs IRIS vs relapsing MS
- Clinical context: emergence of worsening neurologic symptoms typically within weeks to a few months following a period of stability after withdrawal of NTZ.
- MRI typically shows enhancement and enlargement of the PML lesions, which may be associated with surrounding edema and mass effect, however there is no definite way to discriminate IRIS from worsening PML
- In one study of 1H-MRS; Cho/Cr, ml/Cr, Lipid/lactate /Cr were increased and NAA/Cr decreased in PML-IRIS compared to PML without IRIS. Persistent elevation of ml/Cr ratio was seen with PML-IRIS. Combined lipid lactate peaks / Cr >1.5 when combined with contrast enhancement of lesions, was associated with a 79% probability of IRIS

Natalizumab associated PML IRIS

Enhancement patterns include linear diffuse, faint peripheral and speckled
Patient 5 above had active PML

Images from:

Hyperperfusion assessed by arterial spin labeling 3 months following symptom onset has recently been suggested to predict the absence of IRIS

Labeling modified
Management of IRIS

- Eradicate viable infectious pathogens triggering the immune response, this may require a vigorous initial immune response, particularly where as in PML there is no specific therapy
- Reduce inflammatory related damage resulting from excessive immune response, this may require prolonged treatment
- With chronic infections or a need for immune suppression to prevent organ rejection; may need to balance risks of inadequate therapy of the primary condition and intensity of the IRIS in formulating therapeutic strategy

Treating IRIS: Corticosteroids

- One RCT in HIV associated TB IRIS
  - Prednisone 1.5mg/kg/d for two weeks followed by 0.75mg/kg/d for two weeks was more effective than placebo in reducing days of hospitalization and need for outpatient procedures (combined primary endpoint)
  - Steroid group also had significantly greater improvements in symptoms, Karnofsky scores, and a QOL measure at two and four weeks, but not at later time points in the 12 week study.
- Some HIV-TB-IRIS patients experience recurrent symptoms when steroids tapered or withdrawn requiring therapy for months

Corticosteroid Treatment: Natalizumab Associated PML IRIS

- Primary therapy used in anecdotal reports and case series
- Steroids shown to diminish specific JCV cytotoxic T lymphocyte reactivity (and perhaps that of other effector cells) in blood following IVMP in RRMS patients; potentially interfering with CNS entry of effector cells necessary to control infection
- Corticosteroid therapy during IRIS associated with better outcome as measured by EDSS in retrospective review of MedWatch cases
- Most reports used high does IVMP followed by varying doses and durations oral steroid or recurrent IVMP pulses
- Treatment may be necessary for months

Tan IL Neurology 2011;77:1061-1067    Clifford DB Lancet Neurol 2010;9:438-446
Antoniol C. Neurology 2012;79:2258-2264

Maraviroc

- CCR5 antagonist approved as inhibitor for HIV binding and cell entry
- Reported to block recruitment of CCR5+ immune cells
- Recent case report in Natalizumab-associated PML considered at high risk for IRIS
  - 300mg bid started following PLEX
  - No corticosteroids given
  - Two months after onset, d/c associated with cognitive and behavioral worsening and enhancing PML lesions consistent with IRIS
  - Reinstitution led to improvement
  - Serial CSF studies showed decrease in CCR5+ immune cells
  - Tapered with MRI regression to 150 mg bid, then off at 7 mths
  - Patient remained stable; CSF at 10mths JCV negative
- Case report of use in HIV-associated PML after failure of response to 10days steroid Rx associated with subsequent improvement

Mefloquine

- Found to inhibit JCV replication in an in vitro model of JCV infected astrocytes
- Dosage: 250mg /day for three days followed by 250mg once weekly
- Potential CNS toxicity (seizures, delerium)
- Case reports of benefit in HIV associated PML
- One case report of natalizumab associated PML IRIS with recovery when combined with corticosteroids and mirtazapine
- Other case reports show no benefit
- Randomized controlled trial in mixed cohort of PML cases was terminated when planned interim analysis indicated low likelihood of showing a difference between groups on primary outcome of reduction of CSF JCV DNA copy number


Other treatment options: CNS IRIS

- Thalidomide
  - TNF-α antagonist
  - Used successfully in HIV Cryptococcal meningitis IRIS and disseminated TB IRIS recurring with attempted steroid withdrawal
  - 100mg/d with low dose aspirin
- Monteleukast
  - Leukotrine antagonist used in asthma Rx
  - Case reports of successful use in patients with HIV associated IRIS including one with TB IRIS meningitis recurring following steroid withdrawal
  - Well tolerated at 10mg /d

Brunel A-S. AIDS 2012;26:2110-2112
Hardwick C. Sex Transm Infect 2006;82:513-514
Summary

• IRIS is an exuberant immune response to an infectious or non-infectious antigen which, in the context of reversal of immune suppression, results in clinical deterioration not due to worsening of the infection or primary immune process
• The extent of immune suppression, the rate and extent of the reversal, antigen load, and possibly susceptibility factors including host and pathogen genetics, and effects of antimicrobial therapy may influence the occurrence, nature and extent of the inflammatory response
• IRIS has the capacity to cause substantial tissue damage with consequent morbidity and mortality
• The clinical challenge in MS patients is to discriminate IRIS from inadequately treated infection or relapsing MS
• IRIS may persist for lengthy periods requiring prolonged monitoring and therapeutic intervention