Paradoxical Tuberculosis Reactions in Patients without HIV Infection

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Paradoxical TB reaction

• Phenomenon that has been clinically observed in the literature since at least 1955

• Clinical and/or radiologic worsening of a patient’s pre-existing TB while receiving anti-TB medications
  • Occurs in 6-30% of TB infected patients
  • Seen in both HIV infected and uninfected patients
  • Observations are seen in patients treated with TNF-a inhibitors
  • Can lead to increased morbidity and mortality (especially in patients with CNS TB)
• **Range of presentations: Fever, CNS, LNs, Pulmonary**
  • Worsening lymphadenopathy common presentation
  • Patients with HIV (or with immune suppression) at higher risk

• **Predictors of presentation**
  • HIV status, Other types of immunosuppression, Disseminated disease (presence of LAN/positive cultures)

• **Timing of presentation varies**
  • Median of 4 weeks (HIV positive) to 8-12 weeks (HIV negative) from ATT
Paradoxical TB reaction

• **Outcomes**
  - Overall favorable
  - Patients with increased lymphadenopathy at times required surgical drainage and corticosteroids

• **CNS TB**
  - Intracranial tuberculomas progressing leading to clinical deterioration
  - Can require increased immunosuppression with steroids, thalidomide
  - Residual deficits and even death

**Paradoxical TB Reaction**

- Worsening of TB manifestations after initiation of TB medication
- Incidence 6-30%
- Initial improvement with TB medications

**Predictors**
- HIV positivity/Immunosuppression
- Disseminated disease/LAN

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**Immune Reconstitution Inflammatory Syndrome (IRIS)**

- Worsening of manifestations or an abrupt/atypical presentation of infection when HIV patients start ARVs
- Incidence 7-50%
- Successful HIV virologic suppression and microbiologic outcome (paradoxical)

**Predictors:**
- CD4 lymphopenia
- Pre-existing OI
- Shorter treatment of OIs pre-ART
Pathogenesis of Paradoxical TB Reactions

• Current literature primarily consists of clinical observations at this time
  • Role of immunodeficiencies/immune dysregulation
    • Steroid Tapering versus HIV, Infliximab, AutoAbs, TB itself?
  • Observation of increased lymphocyte counts

• Pathogenesis investigation has been primarily in IRIS
  • Exuberant T cell responses
  • Reliant on interplay with myeloid cells (higher proportion of classical monocytes, cytokines associated with monocytes
  • Evidence of inflammasome activation
Immune reconstitution meets infection.... IRIS

HIV+

Mycobacterial infection

No CD4+ T cells

Resting macrophage

Poor pathogen control

Primed macrophage

Accumulation of primed macrophages waiting for T cell help for full activation

CD4+ T cells introduced

TNF

Excessive inflammation and tissue destruction

IL-6

Others

Barber et al. Nature Reviews Microbiology, 2012
Case of TB IRIS: role of T cells

Pre-ART

IRIS

IFN-γ

TB antigen

Media control

IFN-γ

TNF

0.13

0.375

99.3

0.231

4.67

13.2

79.7

2.48

Slide courtesy of Irini Sereti
Case 1: 36 year old male with HIV+ and TB
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4/15/2015

5/22/2015
Case 1: T cell stimulations
Case 2: 39yoM with CNS TB

Initial Presentation

3 months of ATT
- New Seizures

6 months of ATT
- New Seizures
- On Dexamethasone
- Intensification of ATT

~ 2 years at NIH
- Slow Taper
- Returned to work

Xie et al. OFID. 2019
Case 2:

T cell stimulation

Monocyte stimulation

IFN-γ

IL-1β

TNF

IL-2

IFN-γ

IL-1β

TNF

IL-6

Media only

PPD/irradiated TB

CMV pp65/CMV lysate
Case 3: 55yoF with Disseminated TB

- 55yo Thai lady initially presented with respiratory failure and sepsis and found to have right lung opacification.

- 4 weeks later diagnosed with TB with biopsy of cervical adenopathy in setting of fevers and chills.

- Two weeks of ATT, developed fevers, malaise, and new left upper lobe cavity.

- 11 weeks into therapy developed large draining abscesses, bone lytic lesions, and liver lesions.

- Workup found to have auto-antibody to IFN-γ.
Paradoxical TB reactions

• Pathogenesis is not well understood
  • Primarily clinical characterization without immunologic workup
  • Clinical patterns of paradoxical TB reactions
  • Cases demonstrating an exuberant T cell response at time of reaction

• Diagnosis is made by excluding other causes for worsening TB

• Distinguishing between a paradoxical reaction and treatment failure is important for appropriate management

• Confirming a poor response to anti-tuberculous therapy can be challenging with the time needed to grow TB and difficulty of culturing from extrapulmonary sites
Paradoxical TB reactions: Triton Study

• Goal is to improve understanding of the pathogenesis of this paradoxical reaction in order to assist with diagnosis and treatment options.

• Hypothesis:
  • Pathogenesis driven by immune dysfunction being driven by a high burden of mycobacterial disease and restoration of immune responses upon starting ATT.
    • Immune suppression by TB itself
    • Withdrawal of immune suppression or low drug levels
TRITON: Paradoxical Tuberculosis Reactions in Patients without HIV Infection

• Objectives
  • Characterize immunologic and radiographic responses of TB patients with paradoxical reactions.
  • Investigate whether biomarkers and/or microbiologic burden (using PET and research TB antigen) correlate with paradoxical reactions
  • Exploratory: Drug levels, Auto-antibody production, Transcriptomic studies to look for host predisposition
TRITON: Paradoxical Tuberculosis Reactions in Patients without HIV Infection

• Case Based ARM and Prospective Cohort ARM
  • Criteria for Case Based ARM: Confirmed TB, ATT for 2 weeks, Signs/Symptoms of Paradoxical TB reaction
  • Criteria for Prospective Cohort ARM: Presenting 2 to 4 months after starting ATT to match timing of paradoxical reactions
  • Exclusion HIV infection, pregnancy, breastfeeding, conditions that limit participants' ability to participate in research

• Procedures: Blood draws, apheresis, sputum, PET/CT

• Follow Up: 3 protocol visits (with additional clinical visits as needed for management of issues related to Paradoxical TB reactions)
TRITON: Paradoxical Tuberculosis Reactions in Patients without HIV Infection

- Estimated enrollment is 60, 20 in Case Based ARM and 40 in Prospective Cohort

- For eligible patients, please contact:
  - Maura Manion, MD PI (maura.manion@nih.gov)
  - Frances Galindo, RN SC (france.galindo@nih.gov)

- For HIV+ patients with naïve to ART or with suspected IRIS, please consider PANDORA protocol
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