Paradoxical Reactions/IRIS Diagnosis and Management: A Basic Approach

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Working Definition of Paradoxical Reaction (PR)/IRIS

Diagnosed with confirmed (microbiologically or with molecular methods) or suspected (clinical ± histologic diagnosis) TB with at least one of the following signs/symptoms of a paradoxical inflammatory reaction:

a. Change in physical exam and historical symptoms after initial clinical improvement suggestive of new inflammatory process (e.g., lymphadenopathy or new findings on pulmonary exam)

b. Worsening radiographic evidence of disease after initiation of treatment, as compared with imaging prior to or earlier in treatment

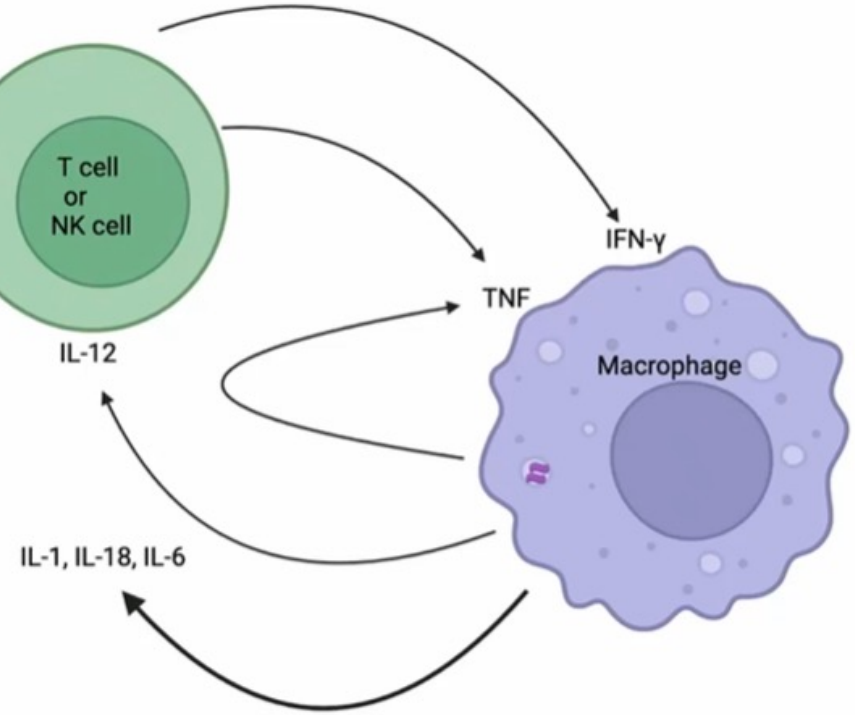
c. Laboratory evidence of acute inflammatory response and/or worsened organ function after initial clinical improvement

AND

The above sign/symptom(s) cannot be explained by microbiologic failure, newly acquired infection, clinical course of a previously recognized infectious agent, side effects of the ATT, the presence of drug resistance, or any other condition except for paradoxical reaction.

Pathogenesis

- High TB burden (higher baseline sputa load correlates with increased risk of PR)
- When lots of antigen present, macrophages continue to be stimulated leading to production of increased proinflammatory cytokines (TNF alpha, IL-1 alpha and beta, IL-6, IL-8, IFN-gamma)
- In HIV-associated IRIS, restoration of cell mediated immunity with anti-retroviral therapy leads to increase of cytokine (IFN gamma and TNF) release



Pathogenesis

- Severely immunosuppressed patients may also be at increased risk: recovery of T-cells in patients with initial lymphopenia may lead to increased risk of PR

- ?Younger age: more robust immune-response after severe TB infection and associated relative immune suppression

- ? PR/IRIS more likely to occur in extrapulmonary disease (more severe in smaller and enclosed spaces such as CNS and spine)

General Principles of Management

- High dose steroids still first option
- Clinical monitoring is most important (new CNS symptoms or weakness/parasthesias/pain) as imaging and common lab monitoring used (e.g., CSF) may be difficult to logistically follow
- Patients may become “steroid-refractory” after prolonged use: due to decreased expression of glucocorticosteroid receptors
- TNF inhibitors are increasingly being used in above cases: probably safe as long as patient remains on TB treatment
- Monitoring CRP and other inflammatory cytokines (ferritin) may be helpful

Other options

Anakinra- IL-1 inhibitor but may be too upstream?

- Ideal because of short half life→ can be withdrawn if cytopenias or other side effects occur
- Need high dose (higher than typically used in RA)
- Adverse events: painful injection sites, cytopenias, increased susceptibility to respiratory tract and skin infections
- Small case series of 7 HIV-neg cases → 2 stopped due to cytopenias
- Effect mostly due to upstream effect on TNF – so may be argument for using TNFi instead

Thalidomide- also IL-1 inhibitor with impact on TNF alpha

- One TBM study with very high dose→ stopped early due to side effects and increased mortality
- Lower dose studied in children- clinical benefit in children with tuberculomas and optochiasmatic arachnoiditis
- Difficult to get in US

TOCILUZUMAB- IL-6 inhibitor

- Used in handful of HIV/IRIS but in 2 cases this followed TNFi use
- ? likely poor CNS Penetration