Outline

• Overview of extrapulmonary disease (EPTB)
• Clinical evaluation and treatment of EPTB
• Clinical presentations of EPTB through case examples
Overview of Extrapulmonary TB

- Worldwide, between 10-25% of TB infections occur in extrapulmonary sites (outside the lung)
- TB can occur in any site, including:
  - Pleura (most common)
  - Lymph nodes
  - Bones and joints
  - CNS (usually meningitis, but can occur in brain or spine)
  - Larynx
  - Pericardial
  - Abdominal sites; Kidneys
  - Genitourinary tract
  - Disseminated (miliary)
Extrapulmonary TB

- Especially common in children and people living with HIV
- EPTB occurs ~10% in HIV(-)
- But in HIV(+),
  - 33% with extrapulmonary alone
  - 33% with pulmonary alone
  - 33% both pulmonary and extrapulmonary
    (many with negative CXRs)
Medical Evaluation of Extrapulmonary TB

- Symptoms of disease (what and how long)
- History of TB exposure, infection, or prior disease
- Past TB treatment
- Demographic risk factors for TB
- Medical conditions that increase risk for TB disease
  - HIV
  - Diabetes
  - Other immunosuppression
  - Under-nutrition
Extrapulmonary TB Symptoms

- Can have the same symptoms as people with pulmonary TB:
  - fever, night sweats, fatigue, loss of appetite, weight loss.

- In addition, patients often develop complaints specific to the body site infected with TB. Examples:
  - Blood in the urine (TB of the kidney)
  - Headache/confusion (TB meningitis)
  - Back pain (TB of the spine)
  - Hoarseness (TB of the larynx)
  - Disseminated (miliary) TB may have no localizing signs, may present with anemia, or low platelets
Diagnosis of Extrapulmonary TB

- Physical Exam

- Specimens should be obtained from the suspected sites of involvement
  - AFB smear, culture
  - Drug-susceptibility testing
  - Nucleic acid amplification (NAA) testing
  - Histopathologic examination

- Always evaluate for pulmonary TB: symptom screen, CXR and sputum evaluation, especially in persons with HIV

- Provider-initiated HIV testing
Diagnostic Challenges

- Often more difficult to diagnose extrapulmonary TB
- Because it EPTB is less common, doctors often first think of other causes for the patient’s symptoms
  - E.g., pain in the right ankle more likely a sprained ankle than TB of the joint
- Secondly, EPTB often occurs in body sites that are difficult to access (e.g., the liver, which cannot be touched, or examined easily).
- Resource-limited settings may not have diagnostic capability to obtain clinical specimen for testing EPTB
Transmission of Extrapulmonary TB

Outside the lungs (extrapulmonary) usually not infectious, unless person has:

- Concomitant pulmonary disease,
- Extrapulmonary disease in the oral cavity or larynx, or
- Extrapulmonary disease with open site, especially with aerosolized fluid.
Major Goals of TB Treatment

1. Cure patient, minimize risk of death/disability, prevent transmission to others
2. Provide safest, most effective therapy in shortest time
3. Prescribe multiple drugs to which the organisms are susceptible
4. Never treat with a single drug or add single drug to failing regimen
5. Ensure adherence and completion of therapy
Treatment of Extrapulmonary TB

- In most cases, treat with same 4 drug regimens used for pulmonary TB
- Culture-negative TB/ (culture not done)
  - Failure to isolate M. TB from person with clinical evidence does not exclude TB
  - If high likelihood of TB, initiate therapy with INH, RIF, PZA, and EMB

Treatment of Extrapulmonary TB

- Special considerations for therapy
  - Disseminated TB or TB meningitis in children: treat for 9–12 months
  - For bone and joint TB, 9 months favored
  - Treat HIV+ patients with EPTB same as with pulmonary only TB, 6-9 months based on clinical factors (disseminated disease, cavitary pulmonary disease with slow response to therapy, etc.)
  - In tuberculous meningitis, ethambutol should be replaced by streptomycin.


Treatment of Extrapulmonary TB

- Although sometimes required for diagnosis, surgery plays little role in the treatment of extrapulmonary TB.
- It is reserved for management of late complications of disease such as:
  - Hydrocephalus
  - Obstructive uropathy
  - Constrictive pericarditis
  - Neurological involvement from Pott’s disease (spinal TB).
- For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage appear beneficial.

Use of Steroids in Extrapulmonary TB

- Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis

 Monitoring and Follow-up

• Assess patient’s response to treatment:
  – Clinical evaluation, bacteriological examination if possible, chest radiograph (if pulmonary as well)
  – As in pulmonary smear-negative disease, the weight of the patient is a useful indicator

• Conduct clinical evaluations at least monthly; after 2 months of therapy, if symptoms do not resolve, reevaluate for
  – Potential drug-resistant disease
  – Non-adherence to drug regimen
  – Other cause of clinical presentation if M. tuberculosis not confirmed
Extrapulmonary TB Cases and Discussion
Extrapulmonary TB Case 1
A neck mass

Presentation

Sept 2011:

- 80 year old male Caucasian on 20-60mg prednisone for biopsy-negative giant cell arteritis (GCA) seen in rheumatology for 6 weeks:
  - Enlarging non-tender cervical and supraclavicular lymphadenopathy (LAD)
  - >10 pound weight loss, severe fatigue and drenching night sweats

- Review of symptoms (ROS) otherwise chronic productive “throat clearing” but no cough

Source: Elizabeth A. Talbot MD, TB Lymphadenitis, New Hampshire Department of Health and Human Services & Dartmouth
Extrapulmonary TB Case 1

Social History

- Married, retired neurologist
  - Healthcare career in Boston MA without known TB exposure
  - Many international trips to provide medical education
    - Lectures in hospitals and clinics, rounding
    - Africa, Southeast Asia, South America, not Former Soviet Union
  - Repeatedly negative tuberculin skin tests (TSTs)
  - Smoker, no drug use, moderate alcohol

Source: Elizabeth A. Talbot MD, TB Lymphadenitis, New Hampshire Department of Health and Human Services & Dartmouth
Extrapulmonary TB Case 1

Rheumatology Evaluation

- PE: afebrile, anxious-appearing regarding differential diagnosis
  - Confirmed weight loss
  - Non-tender, mobile anterior cervical and supraclavicular LAD
  - Lungs clear to auscultation

- Labs WBC normal, erythrocyte sedimentation rate (ESR) 100, Liver function tests (LFTs) normal and HIV negative

Source: Elizabeth A. Talbot MD, TB Lymphadenitis, New Hampshire Department of Health and Human Services & Dartmouth
Extrapulmonary TB Case 1

- Chest x-ray showing wide mediastinum and possible small right apical lung nodule

Source: Elizabeth A. Talbot MD, TB Lymphadenitis, New Hampshire Department of Health and Human Services & Dartmouth
Extrapulmonary TB Case 1

- CT scan image showing extensive necrotic lymphadenopathy in supraclavicular superior mediastinal region with <1cm right apical lung nodule

Source: Elizabeth A. Talbot MD, TB Lymphadenitis, New Hampshire Department of Health and Human Services & Dartmouth
Extrapulmonary TB Case 1

Differential and Investigation

- Differential diagnosis: malignancy vs. sarcoid vs. mycobacterial disease
  - QFT-G strong positive

- Excisional biopsy of right cervical node done
  - Routine, fungal and acid-fast bacilli (AFB) smear negative
  - Mycobacterial culture pending
  - Flow cytology showed no B or T cell clonality
  - Path showed necrotizing granulomas

Source: Elizabeth A. Talbot MD, TB Lymphadenitis, New Hampshire Department of Health and Human Services & Dartmouth
Extrapulmonary TB Case 1

Empiric TB Treatment?

- His physician advocated to start treatment with HRZE based on
  - Pathology
  - Travel
  - Consistent symptoms
- Patient declined
- Continued fever, weight loss, fatigue
  - Excisional site healed well
- AFB culture-positive day 23
  - Probe positive for MTBC
- Begun on INH, RMP, PZA, EMB

Source: Elizabeth A. Talbot MD, TB Lymphadenitis, New Hampshire Department of Health and Human Services & Dartmouth
TB Lymphadenitis

Epidemiology

- TB lymphadenitis represents 30% of EPTB;
- Represents reactivation at site seeded hematogenously during primary TB

- Epidemiology
  - Peak age from children, to 30-40 years old
  - Female to male ratio: 1.4 to 1
  - HIV-infected
  - Asians/Pacific Islanders

Source: Elizabeth A. Talbot MD, TB Lymphadenitis, New Hampshire Department of Health and Human Services & Dartmouth
TB Lymphadenitis

Typical Presentation

• Most often presents as isolated chronic, non-tender unilateral mass in ant or post cervical triangles
  – Firm discrete mass or matted nodes fixed to surrounding structures
  – Multiple nodes may be involved
  – Overlying skin may be indurated
  – Uncommon: fluctuance, draining sinus; bilateral involvement

• Differential diagnosis Non-tuberculous mycobacteria, other infections, sarcoid, neoplasm
TB Lymphadenitis

Primary Diagnostic Tests

- Fine needle aspirate is safer but less sensitive than biopsy
  - ~50% sensitive and 100% specific
  - Combining both cytology and microbiology can increase sensitivity to 91%

- Nucleic acid amplification tests (NAAT) are underutilized
  - Automated NAAT (Xpert) active study is underway
Lymphatic TB Treatment

Treatment

- A six-month regimen including HRZE (two months HRZE, four months HR) is recommended.
- Although the disease is pauci-bacillary, the development of nodes during therapy or at the end of therapy is common.
- Usually there is no evidence of bacteriological relapse.
- No role for steroids except perhaps in unusual circumstances of IRIS with HIV co-infection.
TB Lymphadenitis

Known historically as “scrofula” or the “King’s Evil”, this refers to TB of the superficial lymphatics usually of the neck.
HIV & TB: Adenitis
HIV & TB: Adenitis
1° TB: Adenitis
Extrapulmonary Case 2
Extrapulmonary TB Case 2

History of Present Illness

• 40 year old woman who immigrated from Ethiopia in October 2010

• Admitted with malaise, abdominal pain, shortness of breath, cough, 18kg weight loss (11/2010)

• Diagnosed with HIV infection, CD4 count of 10

• CT Chest, abdomen, pelvis: large pleural effusion, necrotic abdominal and retroperitoneal nodes, liver and splenic lesions, ascites

Source: Michelle Paulson, M.D. Disseminated TB in An Immunocompromised Host, March 15, 2012
Extrapulmonary TB Case 2

CT Scan Chest/Abd/Pelvis 11/2010

Source: Michelle Paulson, M.D. Disseminated TB in An Immunocompromised Host, March 15, 2012
Extrapulmonary TB Case 2

Clinical course of her illness

• Retroperitoneal lymph node biopsy (12/2/10)
  – Pathology: histiocytes with intracellular acid fast bacilli, no caseous necrosis “suggestive of M. avium intracellulare”

• Discharged to hospice

• Son to be put up for adoption

Source: Michelle Paulson, M.D. Disseminated TB in An Immunocompromised Host, March 15, 2012
Extrapulmonary TB Case 2

Referred to District of Columbia (DC) TB Clinic

- 1/13/11: physician notified that culture of pleural fluid from 11/29/10 positive for MTBc
  - Susceptible to all first line drugs (pan-sensisitive)
- 1/13/11: admitted to hospital; sputum smears x 3 negative
- 1/14/11: started RIF 600mg, INH 300mg, PZA 1000mg, EMB 800mg (weight 37 kg)
- Discharge meds RIF/INH/PZA/EMB,
  - As well as other medications including ART
- She eventually improved and regained custody of her son

Source: Michelle Paulson, M.D. Disseminated TB in An Immunocompromised Host, March 15, 2012
Pleural Tuberculosis

- Second most common site of extrapulmonary TB
- ~4% of US cases, up to 20% in other countries where HIV common
- Rupture of sub-pleural focus into the pleural space with inflammatory response
- Symptoms: pleuritic chest pain, SOB, fever
- HIV-infected more likely to have +smear/culture and +pleural biopsy

Pleural effusion:
- Unilateral
- Exudative, lymphocytic
- pH 7.3-7.4
- Smear positive <5%
- Culture positive <50%

Pleural biopsy
- Pathology and microbiology combined sensitivity 65-95%
Pleural Tuberculosis

- Adenosine deaminase (ADA) level
  - Overall several meta-analyses show sensitivity of ADA around 91% and specificity 89%
  - Similar performance in HIV infected
- Cochrane review 2007 of steroids in TB pleurisy
  - No evidence that steroid use improved mortality or residual fluid or adhesions at 8 weeks (only quicker resolution of symptoms less residual pleural thickening)
  - 1 study in HIV+ persons – Possible increased Kaposi sarcoma

Krenke and Korczynski Curr Opin Pulm Med 2010 Baba K et al. PLOS One 2008
Case 3 and 4 Extrapulmonary TB
Case 3-Female GU TB

January 2010:

- 33 year old woman, immigrated from Bangladesh in 2006
- Gravida 2 Para 1, young child at home
- IGRA done at beginning of second trimester = positive
- By patient report, went to get CXR but radiologist told her she should wait until after delivered her baby

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
Case 3—Female Genito-urinary TB

February 2010

- Patient admitted for vaginal bleeding at 21 weeks gestation
- Miscarriage
- Placenta sent for pathology

April 2010

- Placenta pathology—AFB negative, *M. tb* culture positive
- Patient now with cough
- Chest X-ray (CXR) - miliary pattern
- Patient started on anti-TB therapy

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss Connecticut Department of Public Health Tuberculosis Control Program
Case 4: Female GU TB

History

- 34 year old physician, immigrated from India in 1994
- History of +TST, last negative CXR in 2003
- Not treated for LTBI because she thought positive test was due to BCG vaccine as a child
- Gravida 1 Para 0, history of fertility issues

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
Case 4: Female GU TB

Clinical Presentation

May 2010:
- Cough, fever and night sweats
- Did not pursue medical attention at this time

August 2010:
- Admitted at 16 weeks gestation with abdominal pain; Subsequent miscarriage
  - CXR = miliary pattern c/w TB
  - Sputums AFB negative, culture positive
- Placenta pathology
  - Necrotic gestational endometrium
  - AFB smear negative
  - PCR + for *M. tb*
Female Genitourinary Tuberculosis

- Rare manifestation of TB disease
- Often involves the fallopian tubes, also the endometrium
- Likely important cause of infertility worldwide (1-17%)
- Other symptoms include: chronic pelvic pain, menstrual irregularities, abdominal masses

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
Genitourinary TB – Treatment

- Treat with a standard regimen- INH, rifampin, PZA, ethambutol
  - Concerns for adverse effects of PZA on the fetus have not been supported by experience
  - PZA is recommended by the WHO and other international organizations
- 6 months usually sufficient
- Surgery usually only needed if large tubo-ovarian abscess

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
Congenital TB (1)

- Rare manifestation
  - Difficult to distinguish from infection acquired after birth
- Transmission in utero can occur 2 ways-
  - Hematogenous spread through the umbilical vein to the fetal liver
  - Ingestion/aspiration of infected amniotic fluid
- Mothers are often asymptomatic

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
Congenital TB (2)

- Symptoms in infant can be nonspecific
- Cantwell criteria:
  - Primary hepatic complex/caseating granuloma on biopsy
  - TB infection of the placenta
  - Maternal genital tract TB and lesions in the infant in the first week of life
- High mortality rate
- Treat infants with four drugs

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
Testing for TB in Pregnant Women

When Should Testing for TB Occur in Pregnant Women?
- As soon as possible if symptoms are present
- For LTBI screening, should be done early in second trimester

What Test Should be Used?
- TST is valid and safe in pregnancy
- IGRAs can be used but limited data on their accuracy in pregnant women

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
Chest X-Rays and Pregnancy

- All TST/IGRA positive patients should have a CXR with abdominal shielding
- Should not be delayed; identification of TB disease has implications for treatment and infection control
- Radiation exposure for 2 view CXR = 0.1mGy
  - 10x lower than 9 month exposure to environmental background
  - This level of exposure considered negligible risk to fetus

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
TB and Pregnancy: Summary

- Untreated TB is more of a risk to the mother and fetus than treating TB
- Pregnant women should be assessed for their TB risk
- TSTs and CXRs are safe during pregnancy
- Treatment for LTBI can prevent development of TB disease and transmission of TB to the fetus or infant

Source: Lynn E. Sosa, MD, Genitourinary Tuberculosis Resulting in Pregnancy Loss
Connecticut Department of Public Health Tuberculosis Control Program
Miliary TB: Clinical Manifestations

- Miliary TB occurs when tubercle bacilli enter the bloodstream and are carried to all parts of the body
- Wide range of presentations
- May include on one extreme ARDS and on the other extreme failure to thrive without fever
- Symptoms may be dominated by whatever organ system is primarily involved
- Typical patient has a febrile wasting syndrome of 2-4 months duration
Miliary TB: Diagnosis

- In the U.S., the typical patient has an underlying disease that has lead to immunosuppression to some degree.
- Non-specific symptoms are the rule
- Rigors are present rarely
- All organs can be involved
- Many findings such as organomegaly are more common in children
CXR Findings in Miliary TB

- CXR shows miliary pattern in more than half of cases
- In those with an initial normal CXR, a miliary pattern will become apparent in days to weeks later
- The size of nodules is generally 1-3 mm
- 25% to 30% have a focus of chronic TB
Miliary TB: Diagnosis

- Sputum smear is positive in about 25% of cases in both HIV and non-HIV patients.
- In sputum smear neg miliary TB, bronch led to an immediate diagnosis in 65% and this increased to 79% with culture.
- Nucleic acid amplification (NAAT) has not been studied.
Miliary TB: Prognosis

- Prognosis is related to co-morbidity and those factors that lead to a delay in diagnosis.
- HIV patients respond to treatment in a similar fashion to non-HIV patients.
- 20% mortality is found and this has been stable for 30 years.
- Delay in diagnosis is the key factor in mortality of miliary TB.
Additional Sites of Extrapulmonary TB
Bone and Joint TB

- Bone and joint disease due to TB affects all ages but the greatest risk appears to be in those >age of 65y
- Spinal TB or Pott’s is the most common followed by hip and then knee
- Diagnosis is ideally made with isolation of the organism from the affected area
- The diagnosis is supported by
  - Monoarticular disease
  - Cold abscesses
  - Positive PPD
  - Epidemiological risks
  - Chest x-ray with findings consistent with TB
Pott’s Disease
Treatment of Bone and Joint Disease

- Same therapy as for other forms of TB (RIPE)
- Nine months is favored
- Myelopathy with or without functional impairment responds medically
- A randomized trial of the Medical Research Council comparing surgical debridement with multi-drug regimens found no benefit to surgery
- There are instances where surgery should be considered
Tuberculosis of the Spine
Extrapulmonary TB: Take home points

- Not uncommon, especially in HIV-infected persons
- Difficult to diagnose because can mimic many diseases, limited diagnostics in some countries
- Respiratory isolation key until PTB ruled out
- Always get HIV test in patients w/ EPTB.
- Treat it like you would pulmonary TB, except:
  - Steroids in meningeal and pericardial disease
  - Longer treatment in bone/joint TB, TB meningitis, disseminated TB (in children)
Questions?
WHO TB Case Definitions

- The WHO TB case definitions below are based on the level of certainty of the diagnosis and on whether or not laboratory confirmation is available.

- **Tuberculosis suspect.** Any person who presents with symptoms or signs suggestive of TB.

- **Case of tuberculosis.** A definite case of TB (defined next slide) or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment.
  
  - **Note.** Any person given treatment for TB should be recorded as a case. Incomplete “trial” TB treatment should not be given as a method for diagnosis.
WHO TB Case Definitions

- **Definite case of tuberculosis.** A patient with *Mycobacterium tuberculosis* complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay.
  - In countries that lack the laboratory capacity to routinely identify *M. tuberculosis*, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a “definite” case, provided that there is a functional external quality assurance (EQA) system with blind rechecking.
WHO TB Case Definitions

- Cases of TB are also classified according to the:
  - anatomical site of disease;
  - bacteriological results (including drug resistance);
  - history of previous treatment;
  - HIV status of the patient.
WHO TB Case Definitions

• Defining the site of TB important for recording and reporting purposes and to identify the more infectious patients

• **Pulmonary tuberculosis** (PTB) refers to a case of TB involving the lung parenchyma.

• **Extrapulmonary tuberculosis** (EPTB) refers to a case of TB involving organs other than the lungs
  
  – Diagnosis should be based on at least one specimen with confirmed *M. tuberculosis* or histological or strong clinical evidence consistent with active EPTB, followed by decision by clinician to treat with full course of TB chemotherapy.

  – Unless a case of EPTB is confirmed by culture as caused by *M. tuberculosis*, it cannot meet the “definite case” definition given above.

   Can/should still treat presumptively if strong clinical evidence
WHO TB Case Definitions

- If several sites affected, case definition of an EPTB case depends on the site representing the most severe form of disease.
- Miliary tuberculosis is classified as *pulmonary TB* because there are lesions in the lung parenchyma.
- Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, *without* radiographic abnormalities in the lungs, constitutes a case of *EPTB*.
- A patient with both pulmonary and extrapulmonary TB should be classified as a case of *pulmonary TB*. 
First Complication

- 2 weeks into 4-drug therapy
  - Fatigue and anorexia worse
    - Sleeping 18 hours a day!
  - Weight loss and night sweats continue
- Reports to ED where found in new afib
- Admitted and transthoracic echocardiogram shows mod pericardial effusion with RA inversion and impaired RV filling but no tamponade
- Drained 500ml AFB smear negative fluid
- Differential: pericardial TB vs. IRIS?
Tuberculosis Lymphadenitis: Case 1 Medical Course (con’t)

Paradoxical Upgrading Reactions

- Enlarging or new lymphadenopathy ≥10 days into therapy from released mycobacterial antigens
- Relatively common:
  - ~12% mixed population (Blaikley et al. INT J TUBERC LUNG DIS 15(3):375–378)
  - 20-23% of HIV-neg (Fontanilla et al. CID 2011 53: 555)
- Median onset 46d (range 21-139)
- Resolution nearly 4 months
- Controversial role of steroids
- Role of excision vs. aspiration
Tuberculosis Lymphadenitis: Case 1 Medical Course (con’t)

Effectiveness of Corticosteroids in TB Pericarditis

- Systematic review of 4 Randomized controlled trials showed non-statistically significant survival benefit
  - 411 HIV-neg: RR 0.65, 95%CI 0.36 – 1.16; p=0.14
  - 58 HIV-pos: RR 0.50, 95%CI 0.19 – 1.28; p=0.15
- No effect on re-accumulation of effusion or progression to constrictive pericarditis
Tuberculosis Lymphadenitis: Case 1 Medical Course (con’t)

Second Complication

• 4 weeks into 4-drug therapy
  – Faint pruritic maculopapular rash over chest and back
  – Fatigue and anorexia worse; Weight loss and night sweats continue
  – Isolate confirmed as fully susceptible
  – Discontinued INH with some improvement in fatigue, rash

• EMB, RMP, PZA
Tuberculosis Lymphadenitis: Case 1 Medical Course (con’t)

Today

- Asymptomatic, on continuation EMB+RMP
- Six months intended
Extrapulmonary TB Case 2

Clinical Course

- Significant N/V and associated hepatotoxicity (elevated T Bili) and thrombocytopenia
- 02/02/11: RIF stopped and Moxi substituted
- Symptoms and LFTs improved (thrombocytopenia never improved)

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<td>Actions</td>
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IRIS Protocol

- ClinicalTrials.gov (NCT00286767)
- Goal: identify factors leading to IRIS; outcomes of IRIS
- Comprehensive care including H/P, imaging, apheresis, ARV treatment with frequent monitoring, OI screening and PAP smears, RPRs
- Inclusion criteria
  - HIV infected age 18 or greater
  - CD4 count ≤100 cells/ml
  - Not been previously treated with ARVs or have taken them for less than 3 months or none in the past 6 months
  - Must reside within 120 miles of Washington DC area, USA
Extrapulmonary TB Case 2: Clinical course

CT Scan Chest/Abd/Pelvis 2/10/11
Presentation to National Institutes of Health

- String sign
- Bowel edema
- Necrotic node
- Residual loculated pleural fluid
Extrapulmonary TB Case 2
Clinical Course

MRI Brain

2/17/11: Initial MRI Brain

- **Toxoplasmosis (serum):**
  - IgM neg, IgG pos

- **CSF analysis:**
  - Toxoplasmosis PCR: neg
  - CSF not sent for cell count, glucose, protein

- **AFB direct sequencing and AFB culture:** neg
Polling Question?

Would you start steroids?
A. YES
B. NO
Extrapulmonary TB Case 2
MRI Pre- and Post-toxo Treatment

MRIs Brain

2/17/11: Initial MRI Brain
3/24/11: MRI Brain post-toxo treatment
### HIV Treatment

**HIV genotyping: wildtype**

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Antiretrovirals started after TB treatment initiated

6 weeks

Atripla®
(Tenofovir, FTC, Efavirenz)
started 2/24/11
CT Scan CAP 4/13/11

- Increased ascites and lung nodules
- Paracentesis 4/21/11 - 1200cc of fluid
  - WBC 279 (78% lymphocytes)
  - LDH 103 U/L
  - Albumin 2 g/dl
  - Adenosine deaminase 12.5 U/L (ULN 7.6)
  - AFB smear and culture: neg
  - Routine culture: neg

- Thought to be IRIS manifestation
- Prednisone taper 40mg taper (4/29/11-6/24/11)
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<td>60</td>
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<td>TB Rx started (RIPE)</td>
<td>D/C RIF IPMoxi</td>
<td>Start Atripla</td>
<td>Worse CT Steroids</td>
<td></td>
</tr>
</tbody>
</table>
CT Scan CAP 9/7/11

- increased pleural effusion, pulmonary nodules, ascites, LAD
- hepatitis, peak AST 378, ALT 101 associated with N/V

**BAL 9/12/11**
- AFB smear and culture neg
- Fungitell, Histo Ag, Aspergillus Ag, fungal cx neg
- Adeno, RSV, influenza, paraflu neg
- PJP PCR neg, nocardia neg, legionella neg

**Paracentesis 10/3/11**
- Bloody, RBC 46K, WBC 1044
  - (70% lymphs, 4% neuts)
- LDH 132, protein 4.1, albumin 1.6
- AFB smear and culture neg
- Bacterial culture neg

Recurrent IRIS: Prednisone taper, 40mg 10/7/11-11/24/11
## Laboratory Values

<table>
<thead>
<tr>
<th></th>
<th>1/14/11</th>
<th>1/31/11</th>
<th>2/24/11</th>
<th>4/7/11</th>
<th>7/29/11</th>
<th>9/7/11</th>
<th>11/3/11</th>
<th>1/25/12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelet</strong></td>
<td>202</td>
<td>96</td>
<td>132</td>
<td>221</td>
<td>91</td>
<td>120</td>
<td>105</td>
<td>67</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>16</td>
<td>50</td>
<td>14</td>
<td>68</td>
<td>36</td>
<td>101</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td><strong>T. Bili</strong></td>
<td>0.4</td>
<td>2.13</td>
<td>0.6</td>
<td>0.31</td>
<td>0.40</td>
<td>0.6</td>
<td>0.3</td>
<td>0.2</td>
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**IRIS**
TB Follow-up DC DOH / NIH

- Pancytopenic
  - (myelosuppression tends to worsen off steroids)
  - bone marrow biopsy done 2/27/12
  - Mycobacterial culture pending (stain neg) but path
- Positive for small non-necrotizing granulomas
- Weight up to 51.9kg (37.7 kg at start of TB Rx)
- Feels well, started to take classes and work
  - Moved into housing with son
**Pathogenesis**

- Same for pulmonary and extrapulmonary TB

<table>
<thead>
<tr>
<th></th>
<th>Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.</th>
</tr>
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<td></td>
<td>Tubercle bacilli multiply in the alveoli.</td>
</tr>
</tbody>
</table>
A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).
## Pathogenesis

| | Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control (LTBI). |
| | If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone. |
Extra-pulmonary TB and HIV

• In PLHIV, their immune systems cannot respond as strongly to a TB infection so they are not able to contain the TB bacilli outside of the blood stream.

• Primary TB infection is still the lungs, but TB bacilli then access the blood stream and spread through the body, finding other sites to multiply and cause disease.

• Usually TB bacilli remain in the site where they first infected the body and do not gain access to the blood stream, however people living with HIV who are also infected with TB often have TB bacilli in their blood.
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