**Slide 1: Head to Toe: Case Studies of Extra-Pulmonary Tuberculosis**

**Slide 2: Objectives**

Upon completion of this seminar, participants will be able to:

* Describe the clinical features to prompt early recognition and diagnosis of extra-pulmonary TB
* Apply principles of treatment for extra-pulmonary disease to achieve successful patient outcomes
* Discuss the use of appropriate interventions to address challenges in the medical management of extra-pulmonary TB

**Slide 3: Faculty**

* Alfred Lardizabal, MD
	+ Associate Director
	+ NJMS Global TB Institute
* Elizabeth Talbot, MD
	+ Associate Professor, Dartmouth Medical School
	+ Medical Scientist, FIND Diagnostics
* Lynn Sosa, MD
	+ Deputy State Epidemiologist
	+ Connecticut Department of Public Health
* Michelle Paulson, MD
	+ Physician, Science Applications International Corporation—Frederick, Inc.
	+ National Institutes of Health—National Institute of Allergy and Infectious Diseases
* Dana Kissner, MD
	+ Medical Director for Clinical TB Services
	+ Detroit Department of Health and Wellness Promotion

**Slide 4: Agenda**

* Introduction, housekeeping – ***Alfred Lardizabal***
* TB Lymphadenitis – **Elizabeth Talbot**
* Genitourinary TB – **Lynn Sosa**
* TB of the Central Nervous System – **Michelle Paulson**
* TB of the foot—**Dana Kissner**
* Questions and Answers
* Conclusion and wrap up

**Slide 5: Handouts**

You can download slides, sign-in sheet and reference materials at the following link:

http://www.umdnj.edu/globaltb/courses/extrapulmonary-handouts.html

**Slide 6: TB Lymphadenitis**

Elizabeth A. Talbot MD

Deputy State Epidemiologist, New Hampshire Department of Health and Human Services

Associate Professor, Infectious Disease Section, Dartmouth

**Slide 7: Patient Presents**

* Sept 2011: 80M Caucasian on 20-60mg prednisone for biopsy-negative giant cell arteritis (GCA) seen in rheumatology for 6 weeks:
	+ Enlarging nontender cervical and supraclavicular lymphadenopathy (LAD)
	+ >10 pound weight loss, severe fatigue and drenching night sweats
* ROS otherwise chronic productive “throat clearing” but no cough

**Slide 8: 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)
	+ +Tobacco, -drugs, moderate alcohol

**Slide 9: Rheumatology Evaluation**

* PE: afebrile, anxious-appearing regarding differential diagnosis
	+ Confirmed weight loss
	+ Nontender, mobile anterior cervical and supraclavicular LAD
	+ Lungs clear to auscultation
* Labs WBC normal, ESR 100, LFTs normal and HIV negative

**Slide 10: Chest x-ray showing wide mediastinum and possible small right apical lung nodule**

 **Slide 11: CT scan image showing extensive necrotic lymphadenopathy in supraclavicular superior mediastinal region with <1cm right apical lung nodule**

**Slide 12: 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

**Slide 13: Empiric TB Treatment?**

* MD advocated based on
	+ Pathology
	+ Travel
	+ Consistent symptoms
* Patient declined
* Continued fever, weight loss, fatigue
	+ Excisional site healed well
* AFB culture pos day 23
	+ Probe positive for MTBC
* Begun on INH, RMP, PZA, EMB

**Slide 14: TB Lymphadenopathy Epidemiology**

* 20% of all TB in the US is extra-pulmonary (EP) and TB LAD represents 30% of EPTB
	+ 8.5% of all US TB is LAD
* 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: consumptions, genetics, BCG effect?

**Slide 15: Epidemiology of Tuberculosis Lymphadenitis**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Location** | **Date** | **N** | **Median age** | **Female %** | **Foreign-born %** | **HIV+ (n)** | **Pulmonary involved\* (%)**  |
| **Non-TB Endemic** |  |  |  |  |  |  |  |
| California | 1992 | 40 | 38 | 52 | 82 | 11 | 28 |
| Washington DC | 1995 | 8 | 30 | 62 | NA | 0 | 0 |
| Texas | 2003 | 73 | 41 | 62 | 68 | 0 | 0 |
| California | 2005 | 106 | 34 | 66 | 92 | 5 | 0 |
| Minneapolis | 2006 | 124 | 25 | 57 | 100 | 0 | 0 |
| US | 2009 | 19107 | 38 | 58 | 61 | 2102 | 0 |
| Australia | 1998 | 31 | 35 | NA | 87 | 0 | 3 |
| France | 1999 | 59 | 38 | 52 | 69 | 0 | 0 |
| Germany | 2002 | 60 | 41 | 68 | 70 | 0 | 0 |
| UK | 2007 | 128 | 41 | 53 | 90 | 2 | 17 |
| UK | 2010 | 97 | 14-89† | 59 | 90 | 4 | NA |
| **TB-Endemic** |  |  |  |  |  |  |  |
| Taiwan | 1992 | 71 | 42 | 59 | 0 | 0 | 42 |
| Zambia | 1997 | 28 | 24 | 54 | 0 | 0 | 32 |
| Taiwan | 2008 | 79 | 37 | 58 | 0 | 0 | 0 |
| India | 2009 | 893 | 20 | 58 | 0 | 0 | 18 |
| Qatar | 2009 | 35 | 29 | 20 | 86 | 0 | 9 |

NOTE: NA, not available; TB, tuberculosis

\*In some cases, pulmonary tuberculosis is inferred from a positive chest radiograph, but not proven by culture.

†Reflects age range, 57 of 97 patients were between 20-39 years old.

From CID 2011:53

*Data in the above table reflect the speaker’s previous summary that extra-pulmonary TB most frequently occurs in 30-40 year olds, with higher rates in females, people with HIV, and people of Asian descent.*

**Slide 16: Typical Presentation**

* Most common is isolated chronic, nontender LAD
* Firm discrete mass or matted nodes fixed to surrounding structures
	+ Overlying skin may be indurated
	+ Uncommon: fluctuance, draining sinus
* Cervical LAD is most common site of TB LAD
* Unilateral mass in ant or post cervical triangles
	+ Bilateral disease is uncommon
	+ Multiple nodes may be involved
* Differential diagnosis NTM, other infections, sarcoid, neoplasm

**Slide 17: Primary Diagnostic Tests in Tuberculosis Lymphadenitis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Location (year)** | **Culture (+)** | **AFB (+)** | **GI (+)** | **Culture + GI (+)** | **NAAT (+)** |
| **California (1992)** |  |  |  |  |  |
|  Excisional Biopsy | 28/30 (93%) | 11/30 (37%) | 23/30 (77%) | NA | NA |
|  FNA | 18/29 (62%) | 10/29 (35%) | 16/29 (55%) | NA | NA |
| **France (1999)** |  |  |  |  |  |
|  Excisional Biopsy | 12/39 (31%) | 2/39 (5%) | 32/38 (82%) | NA | NA |
|  FNA | 8/26 (31%) | 2/26 (8%) | NA | NA | NA |
| **California (1999)** |  |  |  |  |  |
| FNA | 44/238 (18%) | 58/238 (24%) | 84/238 (35%) | NA | NA |
| **India (2000)** |  |  |  |  |  |
|  Excisional Biopsy | 4/22 (18%) | 5/22 (23%) | 13/22 (59%) | 17/22 (77%) | 15/22 (68%) |
|  FNA | 2/22 (10%) | 4/22 (18%) | 7/22 (32%) | 9/22 (41%) | 12/22 (55%) |
| **California (2005)** |  |  |  |  |  |
|  Excisional Biopsy | 24/34 (71%) | 15/39 (38%) | 31/36 (77%) | NA | NA |
|  FNA | 48/77 (62%) | 5/19 (26%) | 47/76 (62%) | NA | NA |
| **UK (2010)** |  |  |  |  |  |
| FNA | 65/97 (67%) | 22/97 (23%) | 77/97 (79%) | 88/97 (71%) | NA |

* FNA is safer but less sensitive than biopsy
	+ ~50% sensitive and 100% specific
	+ Combining both cytology and microbiology can increase sensitivity to 91%
* NAATs underutilized
	+ Automated NAAT (Xpert) active study

**Slide 18:** **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?

**Slide 19: Paradoxical Upgrading Reactions**

* Enlarging or new LAD >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) and 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

**Slide 20:** **Effectiveness of Corticosteroids in TB Pericarditis**

* Systematic review of 4 RCTS showed nonstatistically 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

**Slide 21: Second Complication**

* 4 weeks into 4-drug therapy
	+ Faint pruritic maculopapular rash over chest and back
	+ Fatigue and anorexia worse
		- Sleeping 18 hours a day!
	+ Weight loss and night sweats continue
	+ Isolate confirmed as fully susceptible
	+ Discontinued INH with some improvement in fatigue and rash
		- EMB, RMP, PZA

**Slide 22: Today**

* Asymptomatic, on continuation EMB+RMP
* Six months intended
	+ Review of 8 papers of treatment of TB LAD showed no difference between 6 and 9 months relapse rates (van Loenhout-Rooyackers et al. Eur Respir J 2000; 15: 192-195)
* Remaining questions

**Slide 23:** **Engraving by André Du Laurens (1558-1609), showing King Henry IV of France touching scrofula sufferers**

**Slide 24: Genitourinary Tuberculosis Resulting in Pregnancy Loss**

* Lynn E. Sosa, MD
* Connecticut Department of Public Health
* Tuberculosis Control Program

**Slide 25: Objectives**

* Describe 2 cases of placental TB associated with miscarriage
* Review female genitourinary TB
* Review the importance of ruling out pulmonary TB when diagnosing and treating extra-pulmonary TB, even during pregnancy

**Slide 26: Case 1- January 2010**

* 33 yo woman, immigrated from Bangladesh in 2006
* G2P1, 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

**Slide 27:** **Case 1- February 2010**

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

**Slide 28: Case 1- 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

**Slide 29: Case 2**

* 34 yo physician, immigrated from India in 1994
* History of +TST, last negative CXR in 2003
* Not treated for LTBI
* G1P0, history of fertility issues

**Slide 30: Case 2- May 2010**

* Patient with cough, fever and night sweats
* Patient did not pursue medical attention at this time

**Slide 31: Case 2- August 2010 (1)**

* Admitted at 16 weeks gestation with abdominal pain
* Subsequent miscarriage
* CXR = miliary pattern c/w TB
* Sputums AFB negative, culture positive

**Slide 32: Case 2- August 2010 (2)**

* Placenta pathology
	+ Necrotic gestational endometrium
	+ AFB smear negative
	+ PCR + for *M. tb*

**Slide 33: 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

**Slide 34: Female Genital TB as a Cause of Infertility**

|  |  |  |  |
| --- | --- | --- | --- |
| **Authors** | **Year** | **Country** | **Incidence in %** |
| Schaffer | 1976 | USA | 1 |
| Padubridi | 1980 | India | 4 |
| Margolis K *et al.* | 1992 | South Africa | 8.7 |
| Emenobolu | 1993 | North Nigeria | 16.7 |
| De Vynck | 1990 | South Africa | 8.7 |
| Tripathy | 2001 | India | 3 |

*The above table shows estimates of female genital TB as a cause of infertility ranging from 1% in the USA to 16.7% in northern Nigeria.*

**Slide 35:** **Female Genital Tract Involvement Resulting in Infertility**

|  |  |
| --- | --- |
| TB ovary | 1.3% |
| Tubo-ovarian mass | 7.1% |
| Pelvic adhesions  | 65.8% |
| Tubal involvement | 48% |
| Endometrial TB | 46% |
| Cervical TB | 5-24% |
| Vulvovaginal TB | Rare case reports |

**Slide 36: Genitourinary TB - Treatment**

* 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

**Slide 37:** **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

**Slide 38:** **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

**Slide 39: 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

**Slide 40:** **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

**Slide 41: 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

**Slide 42: 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

**Slide 43: Thank You!**

**Side 44: Disseminated TB in an Immunocompromised Host**

* Michelle Paulson, M.D.
* SAIC-Frederick, Inc.
* National Cancer Institute at Frederick
* Clinical Research Directorate/CMRP, SAIC- Frederick, Inc., NCI-Frederick, Frederick, MD 21702

**Slide 45:** **History of Present Illness**

* 40 y/o woman who immigrated from Ethiopia in October 2010
* Admitted with malaise, abdominal pain, SOB, cough, 18kg weight loss, 11/2010
* Diagnosed with HIV infection, CD4 count of 10
* CT CAP showed large pleural effusion, necrotic abdominal and retroperitoneal LAD, liver and splenic lesions, ascites

**Slide 46: CT Scan Chest/Abdomen/Pelvis 11/2010**

* Official reading CT CAP 11/25/10:
	+ Large right pleural effusion with compressive atelectasis RML/RLL
	+ Multiple low density areas within enlarged spleen
	+ Multiple enlarged and necrotic retroperitional, perarotic and perportal lymphadenopathy “*c/w lymphoma*”

**Slide 47: Retroperitoneal lymph node biopsy 12/2/10**

* Pathology: histiocytes with intracellular AF bacilli, no caseous necrosis “suggestive of *Mycobacterium avium intracellulare*”
* Discharged to hospice
* Son to be put up for adoption

**Slide 48: Referred to DC DOH TB Clinic**

* 1/13/11: DC DOH notified that culture of pleural fluid from 11/29/10 positive for *MTBc* (pansensitive)
* 1/13/11: admitted to hospital; sputums x 3 negative
* 1/14/11: started RIF 600mg, INH 300mg, PZA 1000mg, EMB 800mg (wt 37 kg)
* Discharge meds RIPE, Azithromycin 1x/week; fluconazole QD; Roxanol prn; MS Contin 15mg QD; Pantoprazole QD, MTV, Bactrim DS QOD

**Slide 49: Referred to DC DOH TB Clinic**

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

|  |  |  |
| --- | --- | --- |
|  | **1/14/11** | **1/31/11 (1st Department of Health draw)** |
| **Platelet** | 202 | 96 |
| **ALT** | 16 | 50 |
| **T. Bili** | 0.4 | 2.13 |
| **Symptoms** |  | N/V |
| **Actions** | TB Rx started (RIPE) | D/C RIF IPE Moxi |

**Slide 50: IRIS Protocol**

* ClinicalTrials.gov (NCT00286767)
* Goal to identify factors leading to IRIS and outcomes of IRIS
* Comprehensive care including H/P, imaging, aphresis, 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

**Slide 51:** **CT Scan Chest/Abd/Pelvis 2/10/11**

* CT reading: Loculated R pleural effusion with atelectasis
	+ A few 1 cm axillary lymph nodes
	+ Marked splenomegaly with few small cyst-like lesions in the spleen and low attenuation masses along the lateral surface of the liver c/w loculated fluid or necrotic nodes
	+ Gallbladder wall thickened
	+ Ascites in left midabdomen associated with multiple dilated loops of small bowel
	+ Bowel wall significantly thickened
	+ Splenic flexure colon markedly thickened with thumbprinting (suggestive of bowel wall edema)
	+ Lumen of transverse colon has been narrowed to string sign
	+ Ascites inflammatory streaks in omentum; necrotic nodes in upper retroperitoneum
	+ Also diagnosed with C. diff colitis at the same time

 **Slide 52: MRI Brain**

* Toxoplasmosis (serum): IgM neg, IgG pos
* CSF analysis:
	+ Toxoplasmosis PCR: negative
	+ CSF not sent for cell count, glucose, protein
	+ AFB direct sequencing and AFB culture: negative

**Slide 53: Polling Question**

* Would you start steroids?

 A. YES
 B. NO

**Slide 54:** **MRIs Brain**

* MRI 2/18: ring enhancing lesion in L basal ganglia 1cm (partially involving the L putamen and globus pallidus. 3 smaller and homogenously enhancing lesions in R parietal lobe cortex, R pons, L cerebellar hemisphere
* MR 3/24: essentially unchanged

**Slide 55: HIV Treatment**

* HIV genotyping: wildtype
* TB treatment started 1/14/11
* 2/15/11: CD4 17, CD4% 3%, viral load 58,434
* Antiretrovirals started 6 weeks after TB treatment initiation. Atripla started 2/24/11
* 2/22/11 & 2/24/11: CD4 32, CD4% 3%, viral load 116,763

**Slide 56: Drug Levels**

* Sent to National Jewish Hospital
	+ Drawn 2-3 hr post dose for INH, PZA, Moxi (*EMB was a pre-dose level*)

|  |  |  |
| --- | --- | --- |
| **2/15/11** | **Level** | **Reference Range** |
| **INH** | 3.21 | 3-6 (2 hours post dose) |
| **PZA** | 30.18 | 20-60 (2 hours post dose) |
| **Moxi** | Trace | 3-5 (2 hours post dose) |
| **EMB** | 0.3 | * 1. (2-3 hours post dose)
 |

* Low Moxi level; MAR reviewed. Patient was taking concurrent magnesium oxide
	+ Magnesium administration times shifted to not w/in 4 hrs of Moxi
* Repeat Moxi level drawn 3 hours post dose; level was 2.22 on 3/8/11

**Slide 57: Therapeutic Drug Monitoring**

* Indicated for:
	+ Treatment failure
	+ Second line drugs
	+ Medical co-morbidities that can result in abnormal pharmacokinetics

**Slide 58: 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: negative
	+ Routine culture: negative
* Thought to be IRIS manifestation
* Prednisone taper
	+ 40mg taper (4/29/11-6/24/11)

**Slide 59: Laboratory Values**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **1/14/11** | **1/31/11** | **2/24/11** | **4/7/11****(IRIS)** | **7/29/11** |
| **Platelet** | 202 | 96 | 132 | 221 | 91 |
| **ALT** | 16 | 50 | 14 | 68 | 36 |
| **T. Bili** | 0.4 | 2.13 | 0.6 | 0.31 | 0.4 |
| **CD4 Absolute/CD4 %** |  |  | 32 (3%) | 60 (6%) |  |
| **HIV VL** |  |  | 116,763 | <50 |  |
| **Sx** |  | N/V |  | Abd girth |  |
| **Actions** | TB treatment started (RIPE) | Discontinue RIF, IPE Moxi | Start Atripla | Worse CTsteroids |  |

**Slide 60: 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 negative
	+ Fungitell, Histo Ag, Aspergillus Ag, fungal culture negative
	+ 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 negative
	+ Bacterial culture negative
* Recurrent IRIS: Prednisone taper, 40mg 10/7/11-11/24/11

**Slide 61: Laboratory Values**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **1/14/11** | **1/31/11** | **2/24/11** | **4/7/11****(IRIS)** | **7/29/11** | **9/7/11****(IRIS)** | **11/3/11** | **1/25/12** |
| **Platelet** | 202 | 96 | 132 | 221 | 91 | 120 | 105 | 67 |
| **ALT** | 16 | 50 | 14 | 68 | 36 | 101 | 20 | 23 |
| **T. Bili** | 0.4 | 2.13 | 0.6 | 0.31 | 0.4 | 0.6 | 0.3 | 0.2 |
| **CD4 Absolute(%)** |  |  | 32 (3%) | 60 (6%) |  | 56 (7%0 | 76 (11%) | 53 (10%) |
| **HIV VL** |  |  | 116,763 | <50 |  | <50 | <50 | <50 |
| **Symptoms** |  | N/V |  | Abdgirth |  | N/V |  |  |
| **Actions** | TB treatment started (RIPE) | Discontinue RIF, IPE Moxi | Start Atripla | Worse CTsteroids |  | Worse CTLFTsBronchSteroids |  |  |

**Slide 62: MRI Brain Improved**

* MRI 2/1/12: decreased intensity and extent of enhancement of L putamen, with residual enhancement and calcification; other tiny enhancing lesions in R parietal cortex, L thalamus, R globus pallidus, B/L cerebellar hemispheres, R pons

**Slide 63: TB Follow-up DC DOH / NIH**

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

**Slide 64: Pleural Tuberculosis**

* Second most common site of extra-pulmonary TB
* Rupture of subpleural focus into the pleural space with inflammatory response
* Symptoms: pleuritic chest pain, SOB, cough, fever
* HIV infected more likely to have + pleural 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 60-95%
	+ Second most common site of extra-pulmonary TB
	+ Rupture of subpleural focus into the pleural space with inflammatory response
	+ Symptoms: pleuritic chest pain, SOB, cough, fever
	+ HIV infected more likely to have + pleural smear/culture and +pleural biopsy

**Slide 65: Pleural Tuberculosis: ADA and Steroids**

* Adenosine deaminase (ADA) level
	+ Overall several meta-analyses show sensitivity 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 (only symptoms)
	+ 1 study in HIV + persons
		- Possible increased Kaposi sarcoma

**Slide 66: Integration of Antiretroviral Therapy with Tuberculosis Treatment**

* Part II of South African study, 429 patients with sputum AFB+ smears and HIV CD4<500
	+ Early=within first 4 weeks of starting TB treatment
	+ Later=within first 4 weeks of continuation phase (CP) of TB treatment
* Bottom line: No significant difference in AIDS / death between groups so ok to defer ARVs until beginning of CP of TB treatment EXCEPT if CD4<50, then there was decrease in AIDS and death with early ARV treatment but significant increase in IRIS
* NEJM 2011;365:1492-501

**Slide 67: Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis**

* 809 patients (North American, South American, Africa, Asia), CD4<250, ARV naïve, TB suspect
	+ “Early”=ARVs within 2 weeks after TB Rx
	+ “Later”=ARVs 8-12 weeks after TB RX
* Bottom line: No significant difference in AIDS defining illnesses or death between groups (unless CD4<50, then lower death / AIDS defining illness with early treatment) but significant increase in IRIS (11% vs. 5%, P=0.002, early vs. late)
* NEJM 2011;365:1482-91

**Slide 68: Earlier vs. Later Start of Antiretroviral Therapy in HIV-infected Adults with Tuberculosis**

* 661 Cambodian patients, CD4<200, ARV naïve, AFB smear +
	+ “Early”=ARVs 2 weeks after TB Rx
	+ “Late”=ARVs 8 weeks after TB RX
* Bottom line: Early ARVs associated with significant decrease in mortality but significant increase in IRIS (including 6 TB-IRIS deaths vs. 0 in late group)
* NEJM 2011;365:1471-81

**Slide 69: Questions/Comments?**

**Slide 70: Acknowledgments**

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**Slide 71: A Sore Foot**

* **46 year old AA man**
	+ Life-long Detroit resident
	+ Diabetes since 1995
	+ Pernicious anemia
	+ Gout
	+ Hypertension
	+ 9/2011 New diagnosis of non-ischemic cardiomyopathy , atrial fib/flutter (cardiac cath / AICD)

**Slide 72: Radiograph of foot**

* October 12, 2011
* Linear lucency along the medial aspect of the first metatarsal may relate to superimposed infection or cellulitis

**Slide 73: The Cure: Surgery**

* 10/12/11 . Pre-op diagnosis: gouty arthritis, right first metatarsophalangeal joint; open wound of right foot.
* Procedure performed: 1. Right 1st metatarsal head resection 2. Excisional debridement of right foot wound.
* Pathology: Consistent with gouty arthritis

**Slide 74: The Elusive Cure**

* 11/27/11 Pre-Op Diagnosis: surgical wound infection/abscess
* Procedure performed: Incision & drainage & debridement to bone
* Pathology: Mixed acute & chronic inflammation, including necrotizing granulomatous
	+ GMS stains for fungi, AFB stains negative

**Slide 75: Two Images Showing Necrotizing Granulomas**

**Slide 76: The Sore Festers**

* Mid-December, 2011 – The patient was in & out of ED, shelters, nursing home
* 12/28 petitioned by shelter for admission
* 1/11/2012 discharged to nursing home
* 1/18 readmitted – remains in hospital today
* Stormy course – fevers, pleural effusion (exudate), renal failure (dialysis), heart failure, respiratory failure
* TB never considered, cultures for mycobacteria never obtained (including from pleural fluid & CSF)

 **Slide 77: February 3, 2012**

* Another of 5 procedures on foot
* Image depicting necrotizing granulomas involving bone

**Slide 78: An Answer**

* BAL, 3 sputums for mycobacteria obtained
* February 10, 11 Sputum 1+ AFB, NAAT + MTB, culture +. QFT .35 on 2/23.
* Image depicting cavity on patient’s CAT scan

**Slide 79: Issues**

* Pathology results
	+ TB not mentioned by pathologists
	+ Clinicians not called by pathologists
	+ Podiatry didn’t see, didn’t recognize significance
	+ Eventually buried in a morass of clinical data that is piling up in our electronic systems
	+ Multiple clinicians failed to find or note the report
* TB not considered
	+ CSF, pleural fluid not sent for mycobacteria cultures

**Slide 80: Questions and Discussion**

* If you wish to ask a question or make a comment:
	+ Un-mute your phone by pressing #6
	+ After your question, re-mute your phone by pressing \*6
	+ Type your questions to host and panelists; priority will be given to verbal questions

**Slide 81: Global TB Institute Medical Consultation Line: 1-800-4-TB-DOCS**

**Slide 82: Thank you for your participation!!**