Medical Update Webinar

Head to Toe: Case Studies of Extra-Pulmonary Tuberculosis

March 15, 2012

New Jersey Medical School Global Tuberculosis Institute

Sponsored by
Global Tuberculosis Institute

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

Faculty

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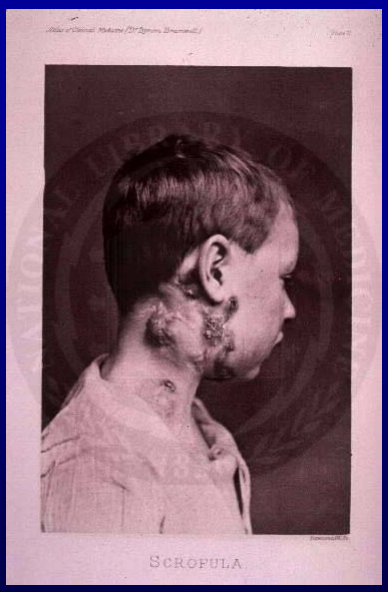

TB Lymphadenitis

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Division of Public Health Services
New Hampshire Department of Health and Human Services

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

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, SEA, South America, not FSU
  - Repeatedly negative TSTs
  - +tob, -drugs, moderate alcohol

Rheumatology Evaluation

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

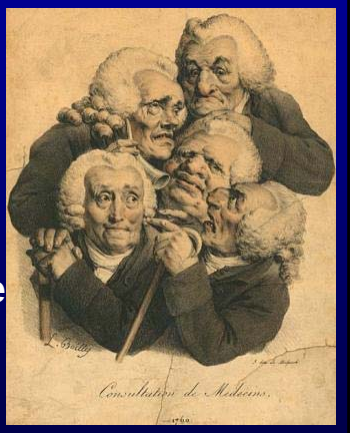
CXR: wide mediastinum and possible small R apical lung nodule

CT scan: extensive necrotic LAD in supraclavicular superior mediastinal region with <1cm R apical lung nodule

Differential and Investigation

- Differential diagnosis: malignancy vs sarcoid vs mycobacterial disease
  - QFTG strong positive
- Excisional biopsy of R cervical node done
  - Routine, fungal and AFB smear negative
  - Mycobacterial culture pending
  - Flow cytology showed no B or T cell clonality
  - Path showed necrotizing granulomas

Empiric TB Treatment?



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

TB Lymphadenopathy Epidemiology

- 20% of all TB in the US is extrapulmonary (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 yo
  - F:M 1.4:1
  - HIV-infected
  - Asians: consumptions, genetics, BCG effect?

Table 1. Epidemiology of Tuberculous Lymphadenitis

Location	Date	N	Mean Age	Female %	Foreign-born %	HIV+ (*n*)	Pulmonary involved* (%)
Non–TB-Endemic							
California [2]	1992	40	38	52	82	11	28
Washington DC [3]	1995	8	30	62	NA	0	0
Texas [4]	2003	73	41	62	68	0	0
California [5]	2005	106	34	66	92	5	0
Minneapolis [6]	2006	124	25	57	100	0	0
US [7]	2009	19 107	38	58	61	2102	0
Australia [8]	1998	31	35	NA	87	0	3
France [9]	1999	59	38	52	69	0	0
Germany [10]	2002	60	41	68	70	0	0
UK [11]	2007	128	41	53	90	2	17
UK [12]	2010	97	14–89⊥	59	90	4	NA
TB-Endemic							
Taiwan [13]	1992	71	42	59	0	0	42
Zambia [14]	1997	28	24	54	0	0	32
Taiwan [15]	2008	79	37	58	0	0	0
India [16]	2009	893	20	58	0	0	18
Qatar [17]	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 and 39 years old.

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

Table 3. Primary Diagnostic Tests in Tuberculous Lymphadenitis

Location (Year)	Culture (+)	AFB (+)	GI (+)	Culture + GI (+)	NAAT (+)
California (1992) [28]					
Excisional Biopsy	28/30 (93%)	11/30 (37%)	23/30 (77%)	N/A	N/A
FNA	18/29 (62%)	10/29 (35%)	16/29 (55%)	N/A	N/A
France (1999) [9]					
Excisional Biopsy	12/39 (31%)	2/39 (5%)	32/39 (82%)	N/A	N/A
FNA	8/26 (31%)	2/26 (8%)	N/A	N/A	N/A
California (1999) [29]					
FNA	44/238 (18%)	58/238 (24%)	84/238 (35%)	N/A	N/A
India (2000) [30]					
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) [5]					
Excisional Biopsy	24/34 (71%)	15/39 (38%)	36/31 (88%)	N/A	N/A
FNA	48/77 (62%)	5/19 (26%)	47/76 (62%)	N/A	N/A
UK (2010) [12]					
FNA	65/97 (67%)	22/97 (23%)	77/97 (79%)	88/97 (91%)	N/A

NOTE. NA, not available; AFB, acid-fast bacilli; GI, granulomatous inflammation; NAAT, nucleic acid amplification test; FNA, fine-needle aspiration.

- 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

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?

Paradoxical Upgrading Reactions

- Enlarging or new LAD ≥10 days into therapy from released mycobacterial antigens
- Relatively common: ~12%* mixed population and 20-23% of HIV-neg**
- Median onset 46d (range 21-139)
- Resolution nearly 4 months
- Controversial role of steroids
- Role of excision vs. aspiration

*Blaikley et al. INT J TUBERC LUNG DIS 15(3):375–378
**Fontanilla et al. CID 2011 53: 555

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

Ntsekhe et al, Q J Med 2003; 96: 593.

Second Complication

- 4 weeks into 4-drug therapy
  - Faint puritic 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

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*
- Remaining questions

*van Loenhout-Rooyackers et al. Eur Respir J 2000; 15: 192-195.

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

Genitourinary Tuberculosis Resulting in Pregnancy Loss

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

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 extrapulmonary TB, even during pregnancy

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

Case 1- February 2010

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

Case 1- April 2010

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

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

Case 2- May 2010

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

Case 2- August 2010

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

Case 2- August 2010

- 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

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

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

Table constructed from: 1. Sharma JB, Roy KK, Pushparaj M, Gupta N, Jain SK, Malhotra N, *et al.* Genital tuberculosis: An important cause of Asherman's syndrome in India. Arch Gynecol Obstet 2008;277:37-41. 2. Sharma JB, Roy KK, Pushparaj M, Kumar S, Malhotra N, Mittal S. Laparoscopic findings in female genital tuberculosis. Arch Gynecol Obstet 2008;278:359-64. 3. Singh S, Gupta V, Modi S, Rana P, Duhan A, Sen R. Tuberculosis of uterine cervix: A report of two cases with variable clinical presentation. Trop Doct 2010;40:125-6. 4. Buppasiri P, Temtanakitpaisan T, Somboonporn W. Tuberculosis at vulva and vagina. J Med Assoc Thai 2010;93:613-5.

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**

Congenital TB

- 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

Congenital TB

- 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

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

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

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

Thank You!

SAIC-Frederick, Inc.
National Cancer Institute at Frederick

Michelle Paulson, M.D.

Disseminated TB in An Immunocompromised Host

Clinical Research Directorate/CMRP, SAIC- Frederick, Inc., NCI-Frederick, Frederick, MD 21702

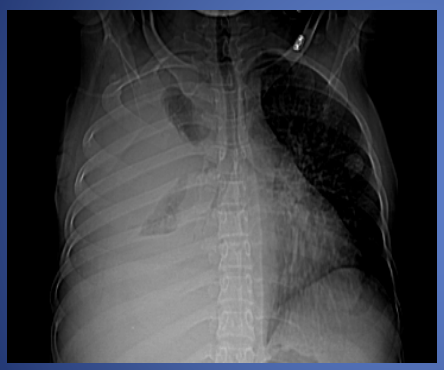
March 15, 2012

SAIC | Frederick

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

CT Scan Chest/Abd/Pelvis 11/2010



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

Referred to DC DOH TB Clinic

- 1/13/11: DC DOH notified that culture of pleural fluid from 11/29/10 positive for *MTBc* (pansens)
- 1/13/11: admitted to hospital; sputums x 3 neg
- 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

Referred to DC DOH TB Clinic

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

1st DOH Draw

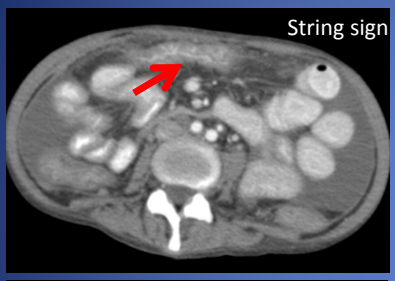
	1/14/11	1/31/11
Platelet	202	96
ALT	16	50
T. Bili	0.4	2.13
Sx		N/V
Actions	TB Rx started (RIPE)	D/C RIF IPEMoxi

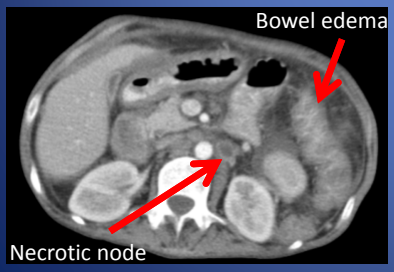
IRIS Protocol

- 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

CT Scan Chest/Abd/Pelvis 2/10/11

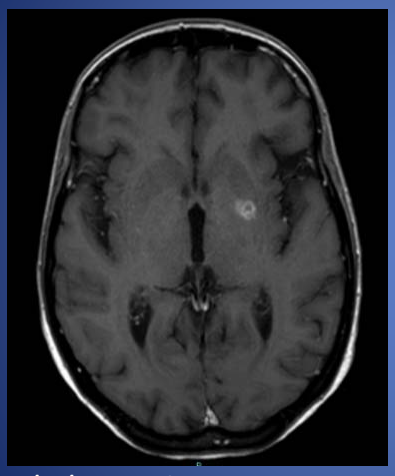
Presentation to National Institutes of Health





Residual loculated pleural fluid

MRI Brain



2/17/11: Initial MRI Brain

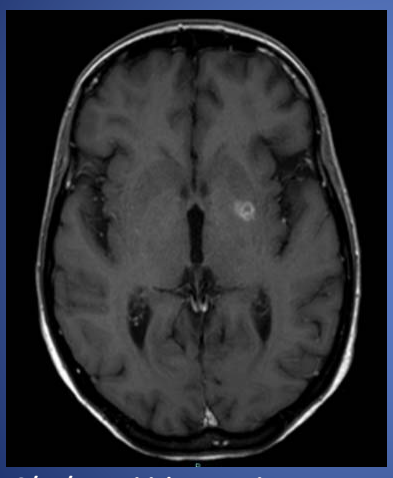
- **Toxoplasmosis (serum):**
  - **IgM neg, IgG pos**
- **CSF analysis:**
  - Toxoplasmosis PCR: neg
  - CSF not sent for cell count, glucose, protein
  - **AFB direct sequencing and AFB culture: neg**

Polling Question?

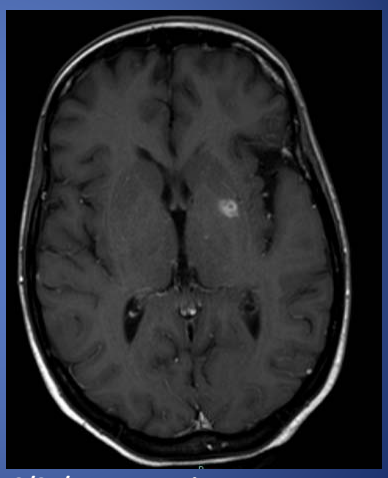
Would you start steroids?

A. YES
B. NO

MRIs Brain



2/17/11: Initial MRI Brain



3/24/11: MRI Brain post-toxo treatment

HIV Treatment

HIV genotyping: wildtype

	CD4	CD4%	Viral Load
TB treatment started 1/14/11			
2/15/11	17	3%	58,434
2/22 & 2/24/11	32	3%	116,763

Atripla® (Tenofovir, FTC, Efavirenz) started 2/24/11

Antiretrovirals started **6 weeks** after TB treatment initiated

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 (2h post dose)
PZA	30.18	20-60 (2h post dose)
Moxi	Trace	3-5 (2h post dose)
EMB	0.3	2-6 (2-3h 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 hrs post dose

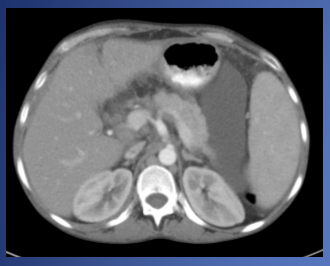
3/8/11	Level	Reference Range
Moxi	2.22	3-5 (2h post dose)

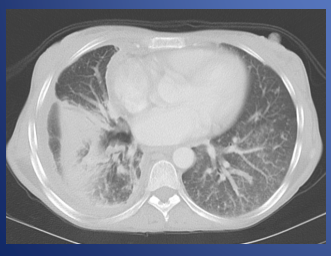
Therapeutic Drug Monitoring

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

Peloquin C. Drugs 2002.
MMWR Treatment of TB 2003.

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)

Laboratory Values

IRIS

	1/14/11	1/31/11	2/24/11	4/7/11	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	0.40
CD4 Abs/ (CD4%)			32 3%	60 6%	
HIV VL			116,763	<50	
Sx		N/V		Abd girth	
Actions	TB Rx started (RIPE)	D/C RIF IPEMoxi	Start Atripla	Worse CT Steroids	

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

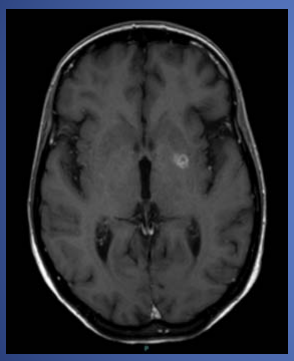
Laboratory Values

IRIS IRIS

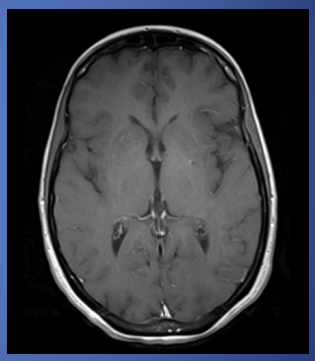
	1/14/11	1/31/11	2/24/11	4/7/11	7/29/11	9/7/11	11/3/11	1/25/12
Platelet	202	96	132	221	91	120	105	67
ALT	16	50	14	68	36	101	20	23
T. Bili	0.4	2.13	0.6	0.31	0.40	0.6	0.3	0.2
CD4 Abs/ (CD4%)			32 3%	60 6%	112 9%	56 7%	76 11%	53 10%
HIV VL			116,763	<50	<50	<50	<50	<50
Sx		N/V		Abd girth		N/V		
Actions	TB Rx started (RIPE)	D/C RIF IPEMoxi	Start Atripla	Worse CT Steroids		Worse CT LFT's; Bronch Steroids		

MRI Brain Improved

2/17/11



2/1/12



TB Follow-up DC DOH / NIH

- Pancytopenic
  - (myelosuppression tends to worsen off steroids)
  - bone marrow biospy 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

Pleural Tuberculosis

- Second most common site of extrapulmonary 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 sm/cx and +pleural biopsy

<u>Pleural Effusion</u>

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

<u>Pleural Biopsy</u>

- Pathology and microbiology combined sensitivity 60-95%

Udwadia and Sen Curr Opin Pulm Med 2010
Gopi at al. Chest 2006

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

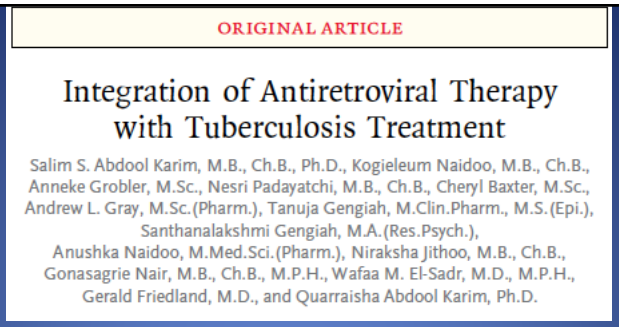
Krenke and Korczynski Curr Opin Pulm Med 2010
Baba K et al. PLOS One 2008

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

Engel et al. Cochrane Database 2007
Elliott et al. J Infect Dis 2004

SAPIT



ORIGINAL ARTICLE

Integration of Antiretroviral Therapy with Tuberculosis Treatment

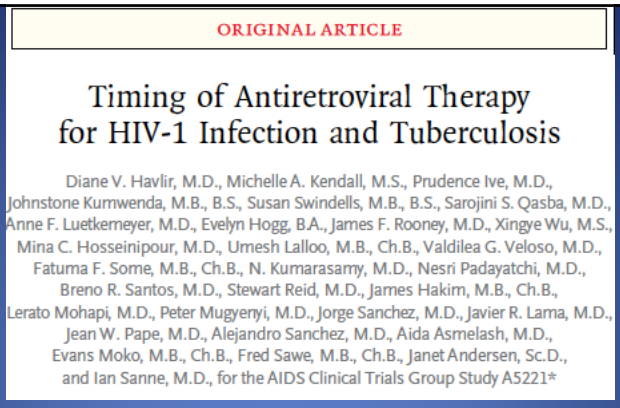
Salim S. Abdool Karim, M.B., Ch.B., Ph.D., Kogieleum Naidoo, M.B., Ch.B., Anneke Grobler, M.Sc., Nesri Padayatchi, M.B., Ch.B., Cheryl Baxter, M.Sc., Andrew L. Gray, M.Sc.(Pharm.), Tanuja Gengiah, M.Clin.Pharm., M.S.(Epi.), Santhanalakshmi Gengiah, M.A.(Res.Psych.), Anushka Naidoo, M.Med.Sci.(Pharm.), Niraksha Jithoo, M.B., Ch.B., Gonasagrie Nair, M.B., Ch.B., M.P.H., Wafaa M. El-Sadr, M.D., M.P.H., Gerald Friedland, M.D., and Quarraisha Abdool Karim, Ph.D.

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

ACTG A5221



ORIGINAL ARTICLE

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

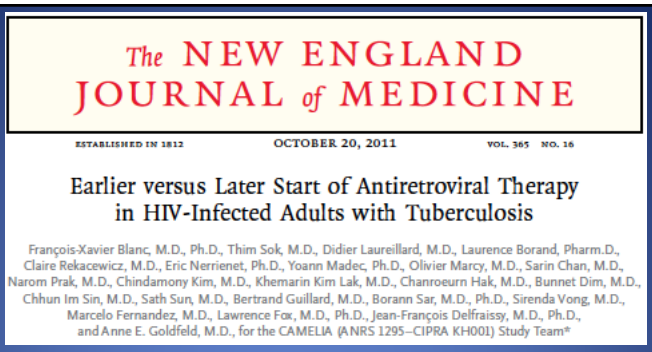
Diane V. Havlir, M.D., Michelle A. Kendall, M.S., Prudence Ive, M.D., Johnstone Kumwenda, M.B., B.S., Susan Swindells, M.B., B.S., Sarojini S. Qasba, M.D., Anne F. Luetkemeyer, M.D., Evelyn Hogg, B.A., James F. Rooney, M.D., Xingye Wu, M.S., Mina C. Hosseinipour, M.D., Umesh Lalloo, M.B., Ch.B., Valdilea G. Veloso, M.D., Fatuma F. Some, M.B., Ch.B., N. Kumarasamy, M.D., Nesri Padayatchi, M.D., Breno R. Santos, M.D., Stewart Reid, M.D., James Hakim, M.B., Ch.B., Lerato Mohapi, M.D., Peter Mugyenyi, M.D., Jorge Sanchez, M.D., Javier R. Lama, M.D., Jean W. Pape, M.D., Alejandro Sanchez, M.D., Aida Asmelash, M.D., Evans Moko, M.B., Ch.B., Fred Sawe, M.B., Ch.B., Janet Andersen, Sc.D., and Ian Sanne, M.D., for the AIDS Clinical Trials Group Study A5221*

809 patients (N.Am, S.Am, 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

CAMELIA



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Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

François-Xavier Blanc, M.D., Ph.D., Thim Sok, M.D., Didier Laureillard, M.D., Laurence Borand, Pharm.D., Claire Rekacewicz, M.D., Eric Nerrienet, Ph.D., Yoann Madec, Ph.D., Olivier Marcy, M.D., Sarin Chan, M.D., Narom Prak, M.D., Chindamony Kim, M.D., Khemarin Kim Lak, M.D., Chanroeurn Hak, M.D., Bunnet Dim, M.D., Chhun Im Sin, M.D., Sath Sun, M.D., Bertrand Guillard, M.D., Borann Sar, M.D., Ph.D., Sirenda Vong, M.D., Marcelo Fernandez, M.D., Lawrence Fox, M.D., Ph.D., Jean-François Delfraissy, M.D., Ph.D., and Anne E. Goldfeld, M.D., for the CAMELIA (ANRS 1295–CIPRA KH001) Study Team*

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

Questions/Comments?

Acknowledgments:

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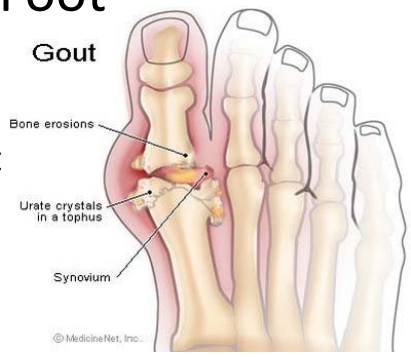
A Sore Foot



- 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)

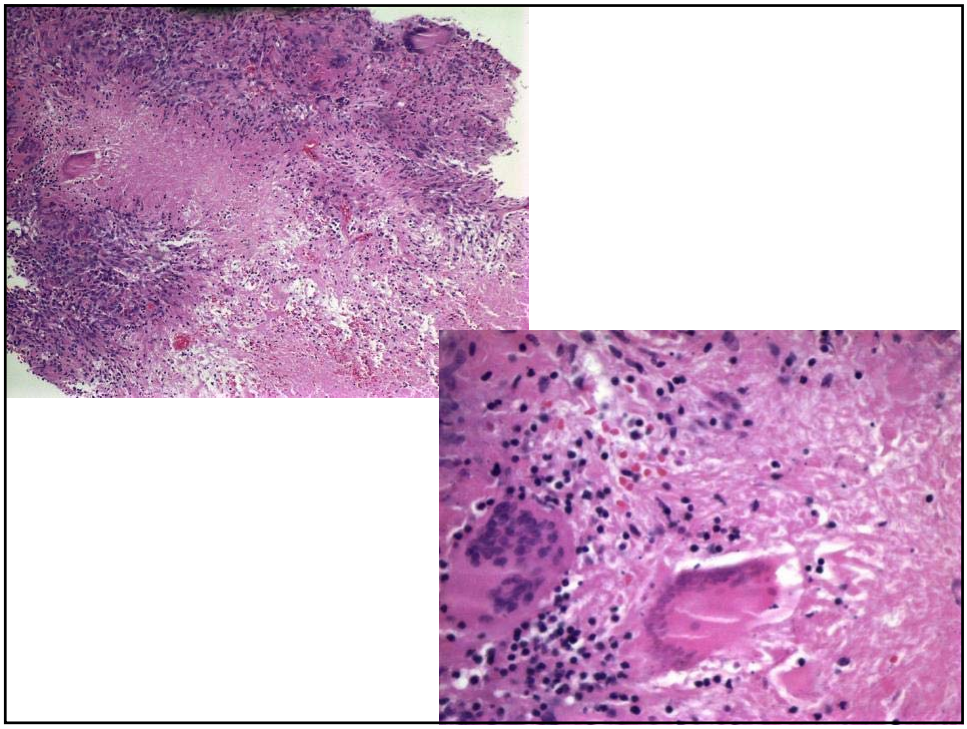
The Cure: Surgery

- 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

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

11/27/2011

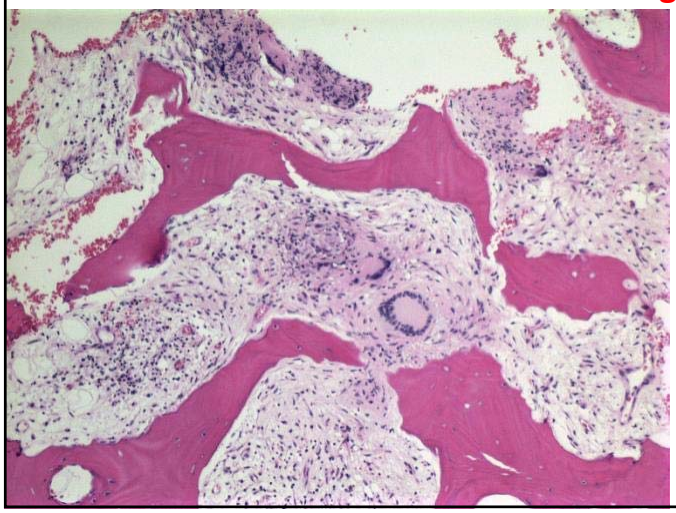


The Sore Festers

- 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)

February 3, 2012
Another of 5 procedures on foot

Necrotizing granulomas involving bone



An Answer

- BAL, 3 sputums for mycobacteria obtained
- February 10, 11 Sputum 1+ AFB, NAAT + MTB, culture +. QFT .35 on 2/23.

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

Thank you for your participation!!