



Mayo Clinic Center for Tuberculosis

Extrapulmonary Tuberculosis 2016



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I have no conflicts of interest, nor a financial interest, arrangement or affiliation with any organization that could be perceived as a conflict of interest in the context of the subject of this presentation.

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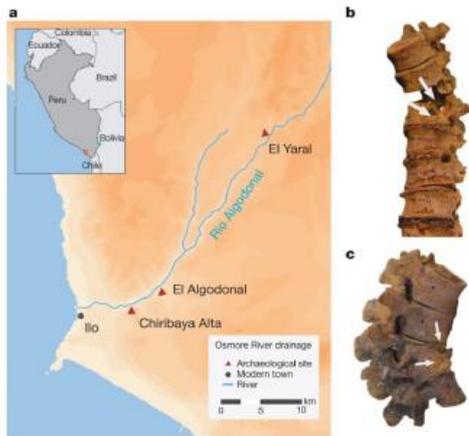


Goals of Talk

1. Identify how the traditional patterns of extrapulmonary compared to pulmonary TB are changing
2. Challenges in diagnosis with extrapulmonary disease
3. Challenges in case management of extrapulmonary disease

Pre-Columbian Mycobacterial Genomes Reveal Seals as a Source of New World Human Tuberculosis

Archaeological description of the skeletal samples.



Kl Bos et al. *Nature* 000, 1-4 (2014) doi:10.1038/nature13591



nature

Extrapulmonary Tuberculosis

- The overall decline in TB cases since 1953 has been almost exclusively due to a reduction in pulmonary TB, with extra-pulmonary TB remaining relatively constant.
- Explanations that have been proposed include:
 - The increased burden of chronic diseases*
 - Immigration patterns*
 - The increase in the use of immune suppressant medications*
 - Certain genotypes of the tubercle bacilli may be linked to a higher risk of extrapulmonary dissemination^

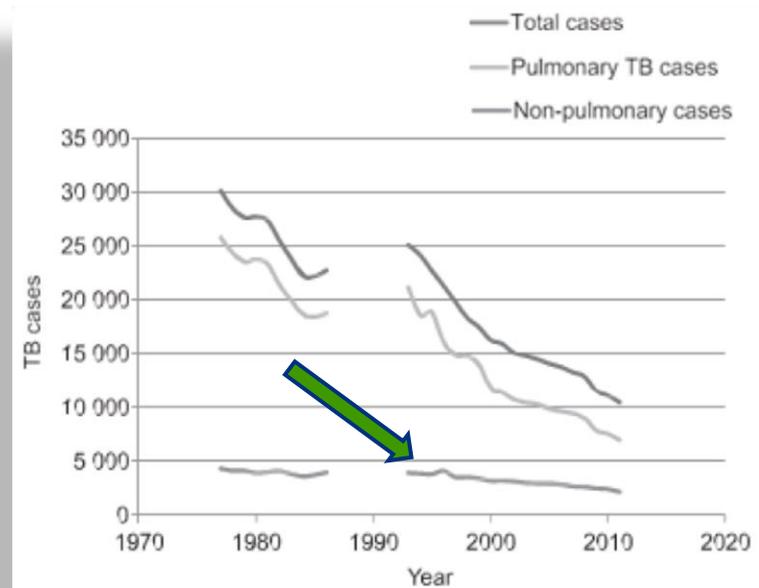


Figure 5 TB cases: pulmonary TB vs. EPTB. EPTB persists, while there is a continuous rapid decline of pulmonary and total TB cases. TB $\frac{1}{2}$ tuberculosis; EPTB $\frac{1}{2}$ extra-pulmonary TB.

Epidemiology of extra-pulmonary tuberculosis in the United States: high rates persist in the post-HIV era, Adada, M. A. Valley,† S. A. Nour,* J. Mehta,* R. P. Byrd, Jr.,* J. L. Anderson,† T. Roy,*
INT J TUBERC LUNG DIS 18(12):1516–1521 Q 2014 The Union
<http://dx.doi.org/10.5588/ijtld.14.0319>

^Different strains of *Mycobacterium tuberculosis* cause various spectrums of disease in the rabbit model of tuberculosis, Manabe YC, Dannenberg AM Jr, Tyagi SK, Hatem CL, Yoder M, Woolwine SC, Zook BC, Pitt ML, Bishai WR, 2003. *Infect Immun* 71: 6004 – 6011.

Clinical Clues for Suspicion of Extrapulmonary Tuberculosis

- Ascites with lymphocyte predominance and negative bacterial cultures
- Chronic lymphadenopathy (especially cervical)
- Exudative pleural effusion with lymphocyte predominance, negative bacterial cultures, and pleural thickening
- HIV infection
- Joint inflammation (monoarticular) with negative bacterial cultures
- Persistent sterile pyuria
- Unexplained pericardial effusion, constrictive pericarditis, or pericardial calcification
- Vertebral osteomyelitis involving the thoracic spine

Extrapulmonary tuberculosis: an overview. MP Golden, HP Vikram, Am Family Physician, 2005 Nov 1;72(9):1761-8.

Long-term mortality in TB Patients: a Danish nationwide cohort study

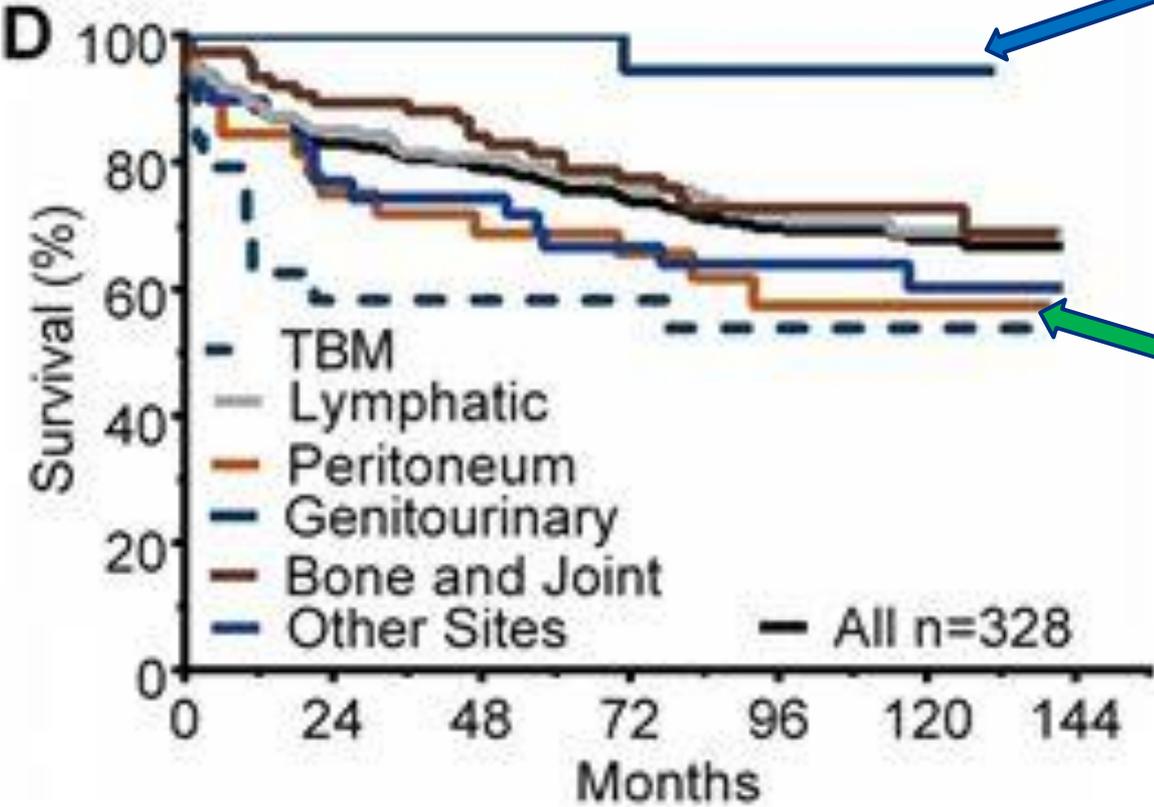
- A nationwide cohort study of all adult Danes notified with PTB or EPTB from 1977 to 2008 and alive 1 year after diagnosis
- A total of 8,291 patients (6,402 PTB and 1,889 EPTB), 24,873 population controls, 1,990 siblings of PTB patients and 11,679 siblings of PTB population controls were included.
- Overall, the mortality rate ratio was:
 - 1.86 (95% confidence interval [CI] 1.77-1.96) for PTB patients
 - 1.24 (95% CI 1.12-1.37) for EPTB patients
- Both cohorts had increased risk of death due to infectious diseases and diabetes.
- Pulmonary TB patients had increased mortality due to cancers, liver, respiratory disease and alcohol and drug abuse.
- The conclusion was that the increase in pulmonary TB patients stem from diseases associated with alcohol, tobacco and drug abuse, as well as immune suppression and family related factors.

Evaluation of Long Term Outcomes of Standard Extrapulmonary TB Treatment

- Retrospective cohort study of all patients treated for EPTB in the state of Texas between January 2000 and December 2005, who had no pulmonary disease.
- Survival compared to persons with latent infection as well as between different types of extrapulmonary TB
- Significant predictors of poor long-term outcome were:
 - Age (hazard ratio for each year of age-at-diagnosis was 1.05 ; CI: 1.04-1.06)
 - Treatment duration
 - Type of EPTB
 - HIV-infection (HR = 2.16; CI: 1.22, 3.83)

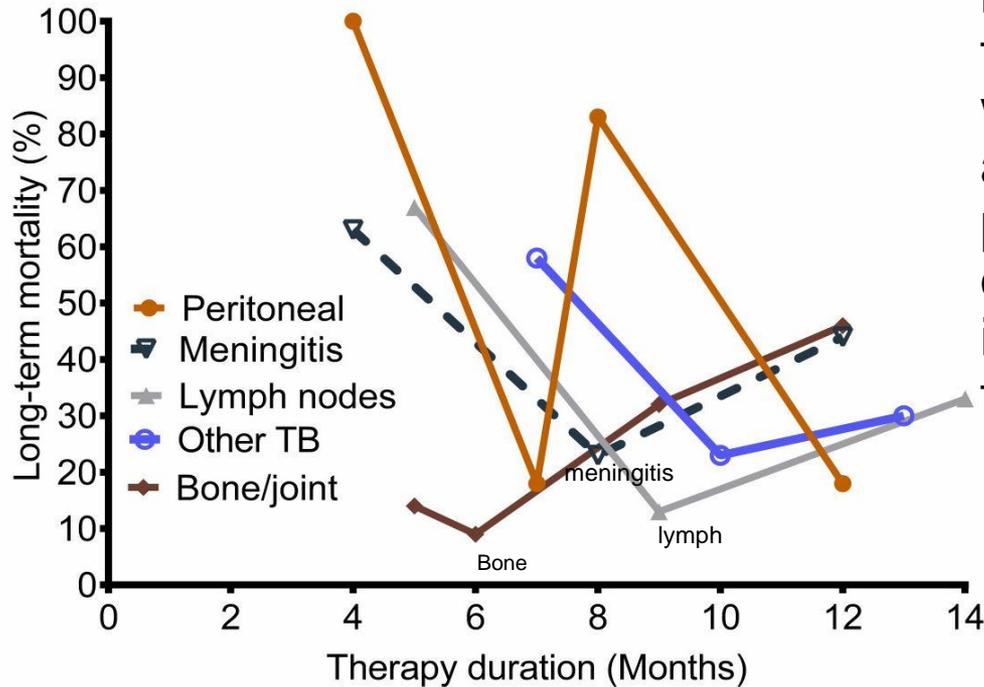
Therapy duration and long-term outcomes in extra-pulmonary tuberculosis. T. Pusch, J. Pasipanodya, R Hall, and T. Gumbo, BMC Infectious Diseases. 14:115, March 1, 2014.

Survival Curves of Different EPTB Types for Patients with Microbiologically Proven Disease



Treatment Duration v Mortality

Figure 5.

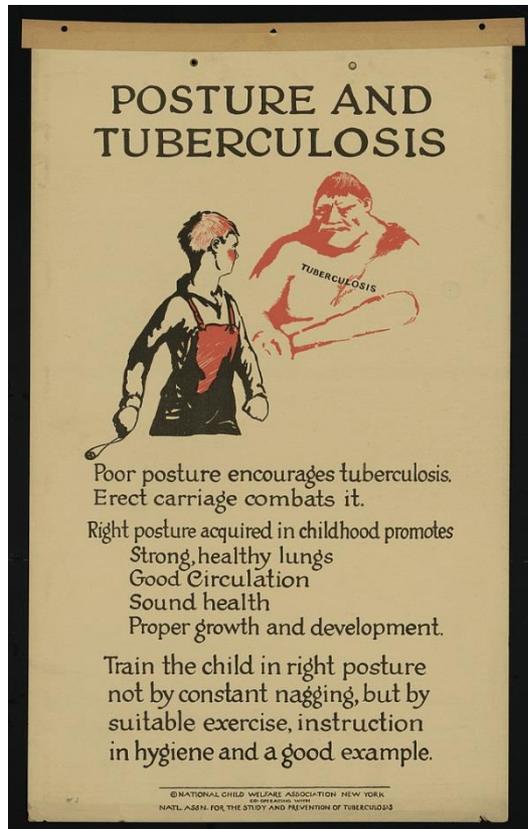


“For all disease syndromes, mortality decreased with longer treatment duration until a nadir, which was the treatment duration associated with lowest proportion of patients with adverse long-term outcomes. Thereafter, mortality increased with longer duration of therapy.”

What Does All This Mean?

- Five year mortality of adequately treated meningitis (46%) and peritonitis (42%) TB is similar to that of **untreated, smear positive pulmonary TB** (42-70%)
 - May reflect TB's damage to different organs in the body
 - May reflect different antibiotic penetration of different organs in the body
 - May indicate that Mtb genotypes that preferentially cause meningitis or peritonitis are more difficult to kill and have a higher propensity to fail or develop drug resistance
- Implies that there is a treatment length duration point associated with a best long-term outcome, and that therapy duration beyond this point leads to poorer survival.
- This was a retrospective study, and findings must be tested in prospective studies.

Differences for Extrapulmonary Tuberculosis: Adjunctive Corticosteroids



- Tuberculous pericarditis?
 - 2014 NEJM study of pericardial TB and the use of glucocorticoids
 - This is now reflected in the new TB treatment guidelines.
- Tuberculous meningitis?
 - Yes, use adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks

Central Nervous System Tuberculosis

- Central nervous system tuberculosis includes tuberculous meningitis (the most common presentation), and intracranial tuberculomas
- Clinical:
 - An initial phase of malaise, headache, fever, or personality change
 - Followed in two to three weeks by protracted headache, vomiting, confusion, and focal neurologic findings
 - If untreated, mental status deteriorates into stupor or coma.
 - Convulsions can occur at all stages of the illness.
- Optimal duration of therapy still not firmly established through randomized controlled trials
- Updated guidelines continue to recommend 12 months of treatment
- Preferred frequency of dosing is once daily for both the intensive and continuation phases.

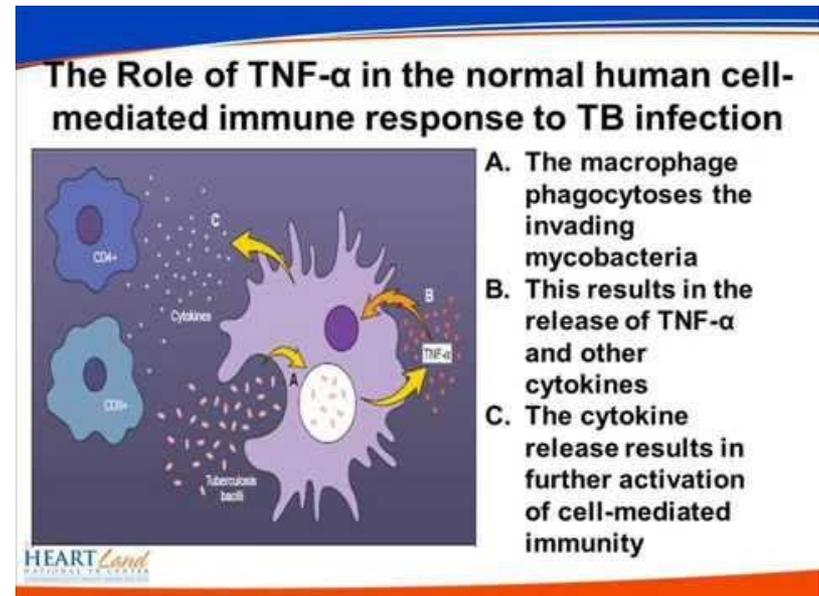
HIV—Unique Features of AIDS Associated Tuberculosis

- Higher rate of disseminated disease
- Higher rate of extrapulmonary tuberculosis
- Rapid progression
- Visceral lymphadenopathy
- Tissue abscesses
- Negative TST

1. Diagnosis and management of miliary tuberculosis: current state and future perspectives. S. Ray, A. Talukdar, S. Kundu, et al., *Therapeutics and Clinical Risk Management*, 9, 9–26, 2013.
2. An Updated Systematic Review and Meta-analysis on the Treatment of Active Tuberculosis in Patients with HIV Infection. F. Khan, J. Minion, A. Al-Motairi, A. Benedetti, A. Harries, D. Menzies, *Clin Infect Dis*. 55 (8): 1154-1163, 2012.

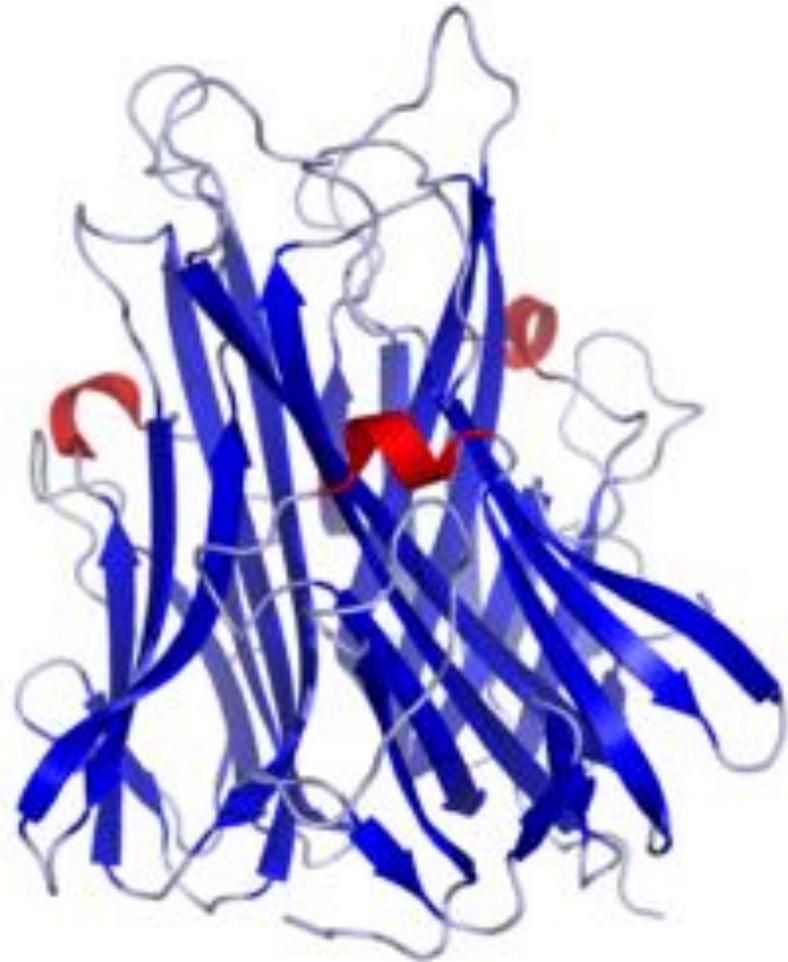
TNF-A INHIBITOR–ASSOCIATED TUBERCULOSIS

- TNF is a cytokine involved in mechanisms that form part of the host response to infection and cancer
- Has a critical role in the pathogenesis of chronic inflammatory diseases such as:
 - rheumatoid arthritis
 - psoriasis
 - ankylosing spondylitis
 - juvenile idiopathic arthritis
 - inflammatory bowel disease
- TNF-a Inhibitor medications include:



TNF- α Inhibitors and Increased Risk of TB

- adalimumab
- certolizumab pe
- Cimzia
- Enbrel
- etanercept
- golimumab
- Humira
- Inflectra
- infliximab
- infliximab-dyyb
- Remicade
- Simponi
- Simponi Aria



Summary of TNF-a Inhibitors and TB

- 4-11x increase in risk for TB in TNF-a Inhibitor patients
- Onset very quick—usually within 18 weeks of starting treatment
- Higher mortality rate due to extrapulmonary and disseminated disease 12-17% mortality rate
- Extrapulmonary more than half; and about one quarter are disseminated cases
- Screen all patients for risk factors and place TST before beginning TNF-a Inhibitors

Children and Extrapulmonary Tuberculosis

- Two main factors determining the risk of progression to disease are:
 - Patient age
 - Immune status
- Neonates have the highest risk of progression to disease:
 - Miliary
 - Meningeal
- Children ages 5-10 less likely to develop disease than other age groups
- Adolescents can present with same picture as adults:
 - Progressive primary tuberculosis
 - Cavitory disease

Children and Presentation of Tuberculosis

- Overall, most common sites of disease in children are intrathoracic and lymphadenopathy.
- Clinical manifestations are often due to a profound inflammatory response to a relatively low burden of organisms.
- This reflects the low yield of diagnostic tests, and diagnosis of TB in children is often based on:
 - Epidemiological linking
 - Positive TST or IGRA
 - Compatible clinical and radiographic presentation



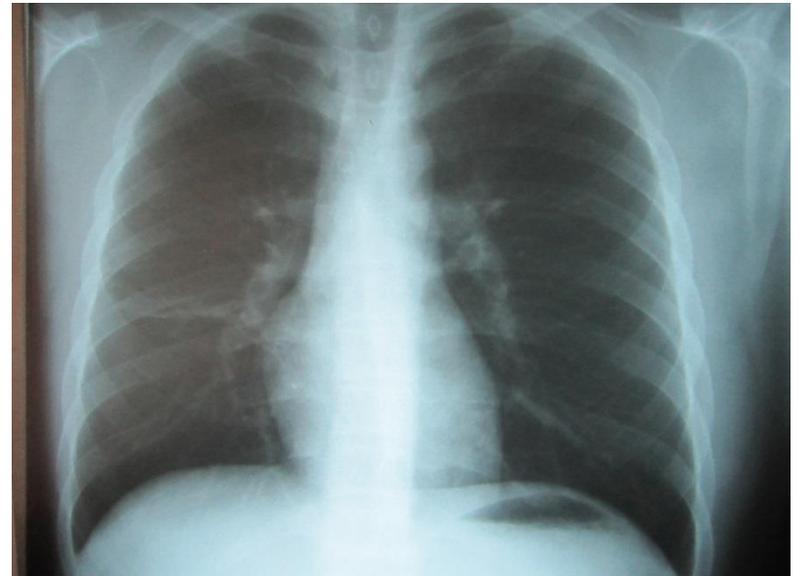
Cervical Lymphadenitis

- Traditionally described as accounting for about 50% of extrapulmonary disease in children.
- Abnormal chest radiographs in 30-40%
- A source case is identified in one half of children
- Often present as solid masses 2-4 cm in size.
 - Lack tenderness, erythema or warmth
 - Untreated nodes caseate and form sinus tracts
 - Paradoxical increase in adenopathy seen about 20% of the time after initiation of treatment.
- Constitutional symptoms such as fever, fatigue and failure to thrive are present about 50% of the time.



- 15 y.o. boy, originally from Vietnam
- Presented to primary care provider with R cervical swelling
- 7/04 CXR for positive TST “Linear opacity in the right mid-lung. Atelectasis or scar are both considered.”
- 8/27 CT of neck shows “pathologic nodes, with low attenuation areas within, near fluid density”
- 10/17 Excision of R Neck mass, showing extensive necrotizing granulomatous inflammation. Smear negative
- 11/20 Tissue culture positive for M tb— Physician and hospital notified by lab
- 11/28 CXR now done for dyspnea. Read as “area of streak atelectasis in the right mid-lung. Summary: Normal Chest”
- 11/28 Referral made to Oakland County Health Division (OCHD)

Lymphatic TB- Diagnosis



Oakland County Health Division

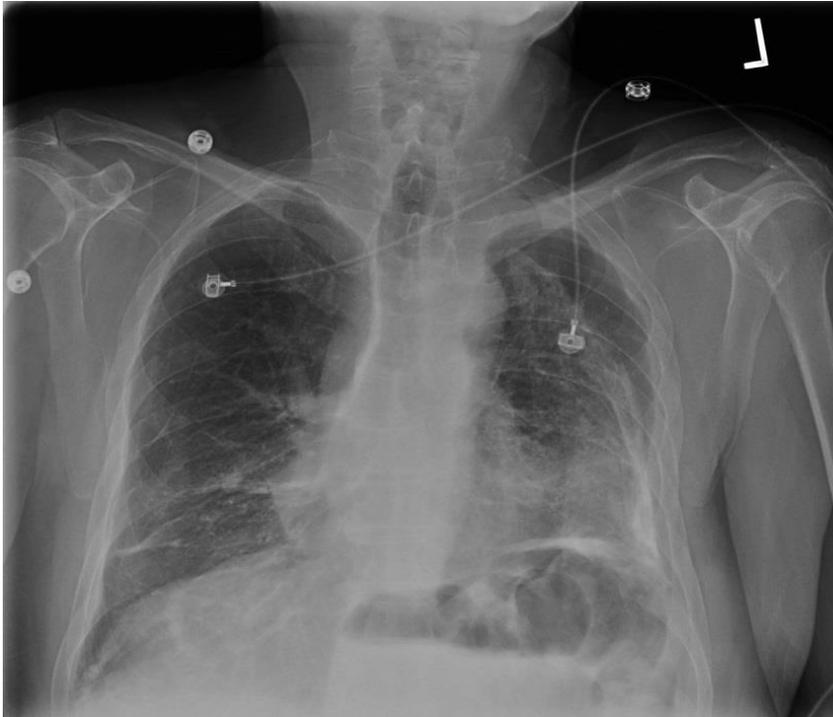
- 11/28 Notified of patient with +Mtb lymph node
- 11/28 Patient seen by TB Case Manager. First sputum collected
- 11/29 second sputum collected, RIPE started with 14 daily doses
- 11/30 third sputum
- 12/18 OCHD notified that first and second sputum +Mtb



Skeletal Tuberculosis

- Symptoms of skeletal TB may include the following:
 - Back pain or stiffness
 - Lower-extremity paralysis, which can be seen in as many as half of patients with undiagnosed Pott's Disease
- Tuberculous arthritis, usually involving only 1 joint
- Bones involved in order of frequency:
 - Vertebrae > knee > hip > elbow > wrist > shoulder

82 Year Old Man With SOB



- Worked up for pulmonary embolism
- History of emphysema with bilateral calcified and noncalcified pleural plaques
- A new perivertebral mass was found with this admission that eroded through the T3 and T4 vertebral bodies

Pott's Disease

- Spinal tuberculosis
- Most commonly involving the thoracic spine
- Infection begins in anterior/inferior aspect of vertebral body
- Destruction of intervertebral disc and adjacent vertebrae
- Creates anterior wedging and angulation of adjacent vertebral bodies



Pott's Disease



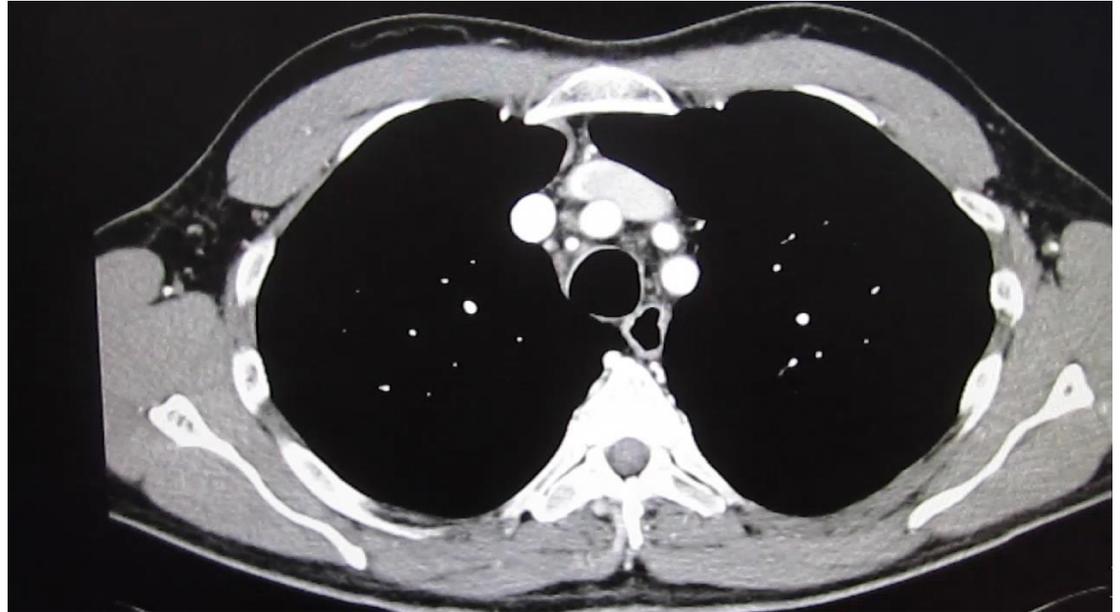
46 y.o. Man with Painful Rib Lesion

- Healthy, no TB risk, public relations professional
- Presented with pain on right side, specific area on anterior right chest
- Initially no other signs or symptoms
- After 4 months developed slight lump at the site of the pain.
- No history of trauma, no radiation of pain



Where Did He Get This?

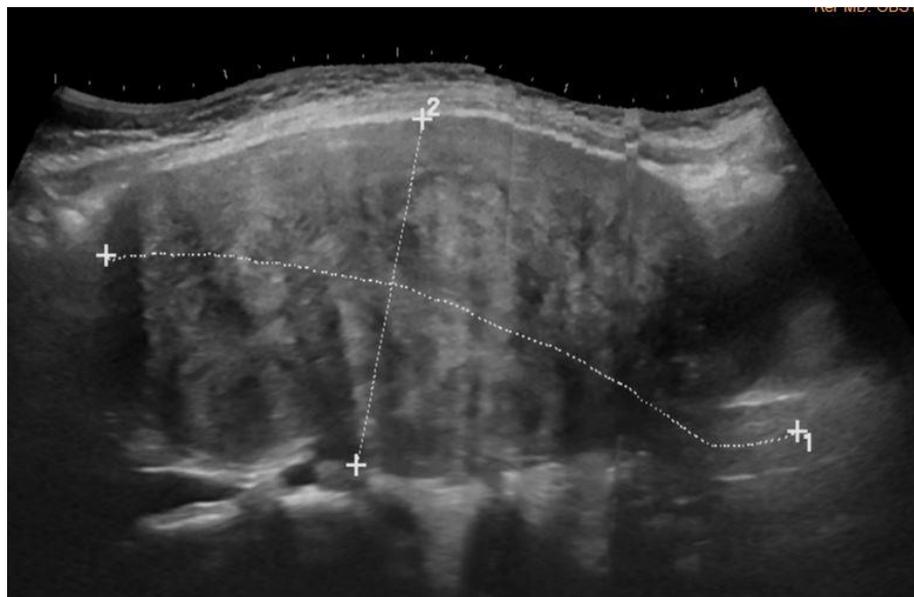
- CT of chest showed axillary, hilar and mediastinal adenopathy
- 3.6 x 2.6 cm destructive lesion of the 8th right rib
- Working diagnosis was malignancy
- Biopsy grew Mtb



Genitourinary Tuberculosis

- Patients usually present with long-standing urinary symptoms.
- Urinalysis usually:
 - Culture negative
 - Pyuria
 - Hematuria
- Lower urinary tract symptoms are usual presenting symptoms and include pyuria, hematuria and pain
- PCR tests helpful for rapid diagnosis but **MUST REQUEST ACID-FAST BACTERIAL CULTURE** for confirmation and drug susceptibility testing.
- Peak occurrence for urogenital TB is between the ages of 20 and 40 years with a 2:1 ratio of men to women.
- GUTB is strongly associated with infertility in women and rates of successful pregnancy remain low even after treatment
- May account for up to 1% of postmenopausal bleeding

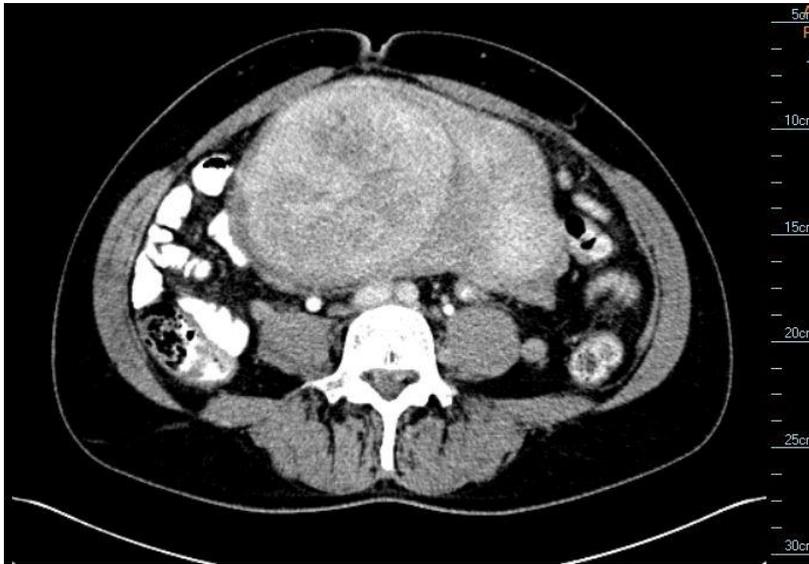
54 y.o. Woman Evaluated for Abdominal Pain and Cramping



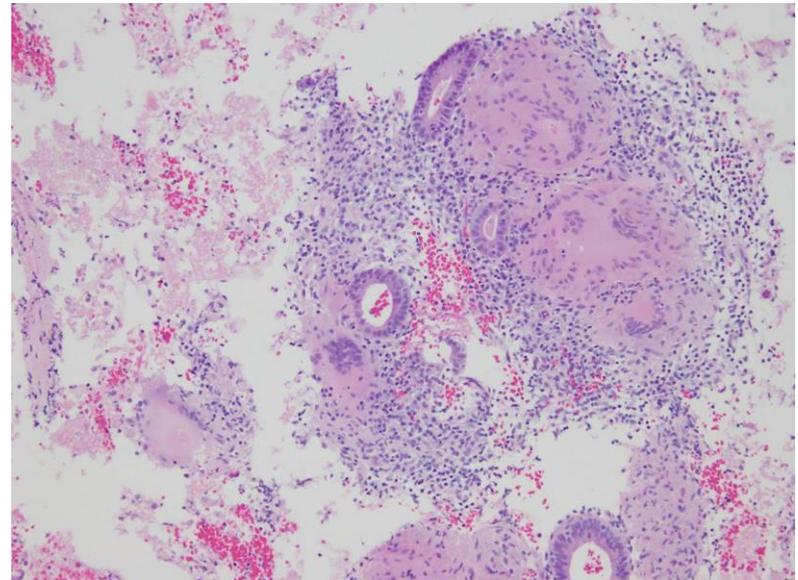
- U/S in December was read as multiple hypoechoic solid myometrial masses, largest measuring 9 cm.
- Likely exposed during childhood in Central America
- TST 15 years ago was positive-not offered treatment
- S/S included night sweats and history of fibroids

Further Studies

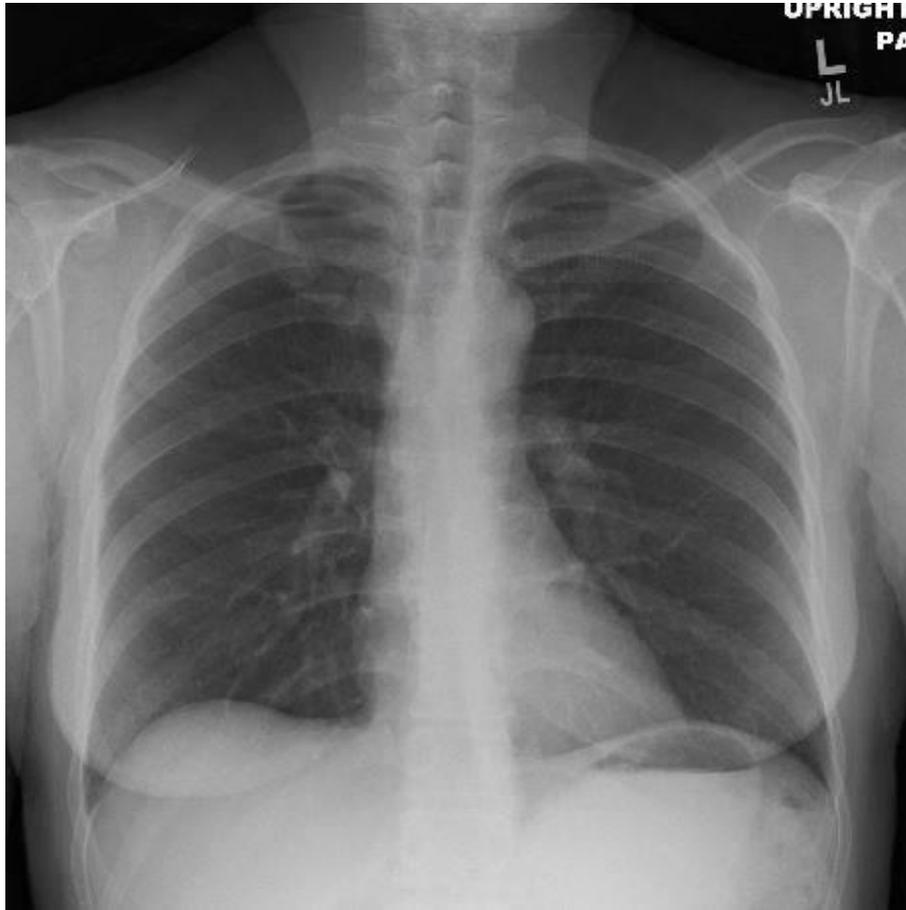
CT of abdomen six months later showed a large heterogeneous uterus measuring 16.8 cm in its greatest dimension, with smaller adjacent satellite lesions



Pathology reported granulomatous endometrium



Extrapulmonary Disease Does Not Exclude Pulmonary Disease

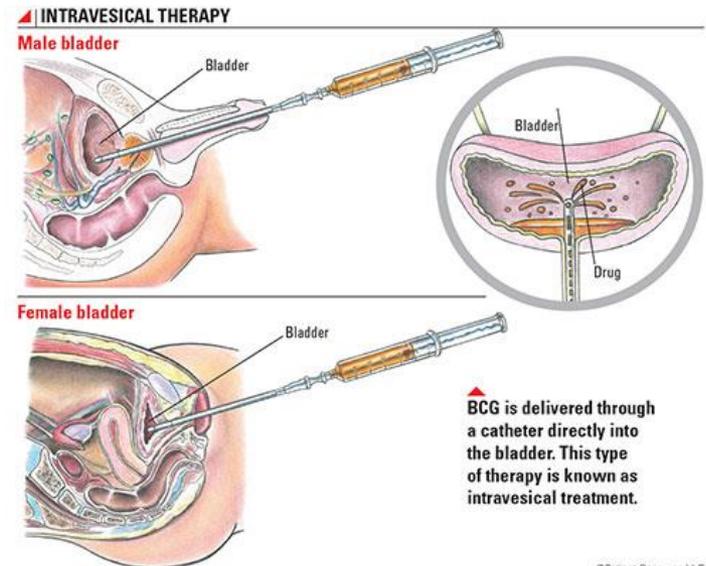


- No address had been put on lab specimens, so lab report of positive Mtb was sent to the county where the lab was located, not the county of residence.
- LPH not contacted by infectious disease specialist as this was “extrapulmonary and not contagious.”
- Three sputums submitted by Oakland County after two weeks of treatment. One positive for Mtb.
- **It’s not excessive, it’s precaution!**

“BCGosis”

or Problems Associated with Intravesical BCG Administration for Bladder Cancer

- Immunotherapy causes the body’s own immune system to attack the cancer cells.
- Bacillus Calmette-Guerin (BCG) is the main intravesical immunotherapy for treating early-stage bladder cancer.
- BCG is put directly into the bladder through a catheter.
- The body’s immune system cells are attracted to the bladder and activated by BCG, which in turn affects the bladder cancer cells.



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- **Case studies:**

- June, 2016: 69 y.o. man had documented miliary pulmonary nodules, penile granulomas and mycotic aortic aneurysms after intravesical BCG treatment
- May, 2016: 75 y.o. man treated for bladder cancer with intravesical instillation of BCG in 2006, had recent worsening of Parkinson symptoms and progressive pancytopenia. Bone marrow biopsy showed a granulomatous inflammatory infiltrate.

- BCGosis can present with severe systemic symptoms.
- Urine culture is usually negative.
- The pathogenic mechanisms underlying the development of complications following BCG instillation are not fully understood
 - Difficult catheterization is a significant risk factor.
 - Hypersensitivity is hypothesized as another factor
 - Underlying immunosuppression does NOT appear to be a risk factor



Works Cited:

- S. Ray, A. Talukdar, S. Kundu, et al., Diagnosis and management of miliary tuberculosis: current state and future perspectives. *Therapeutics and Clinical Risk Management*, 9, 9–26, 2013.
- Manabe, Yukari C., et al. "Different strains of Mycobacterium tuberculosis cause various spectrums of disease in the rabbit model of tuberculosis." *Infection and immunity* 71.10 (2003): 6004-6011.
- MP Golden, HP Vikram., Extrapulmonary tuberculosis: an overview. *Am Family Physician*, 72(9):1761-8, Nov 1, 2005.
- T. Pusch, J. Pasipanodya, R Hall, and T. Gumbo, Therapy duration and long-term outcomes in extra-pulmonary tuberculosis, *BMC Infectious Diseases*. 14:115, March 1, 2014.
- Borekci, Sermin, et al. "Factors Affecting the Tuberculosis Risk in Patients Receiving Anti-Tumor Necrosis Factor- α Treatment." *Respiration* 90.3 (2015): 191-198.
- B.J. Marais, M. Pai. "New approaches and emerging technologies in the diagnosis of childhood tuberculosis." *Paediatr. Respir. Rev.*, 8 (2007), pp. 124–133
- Son, Eugene, Mukerji, Shraddha. Atypical Mycobacterial Lymphadenitis in the Head and Neck of Pediatric Patients. Grand Rounds Presentation The University of Texas Medical Branch, December 19, 2012.
- Lange, Jessica. "Genitourinary Tuberculosis in the USA: An Academic Center Experience and Literature Review." *Journal of Science and Medicine Case Reports*, May 5, 2016.
- Yuan, J. (2015). Genitourinary Presentation of Tuberculosis. *Reviews in Urology*, 17(2), 102–105. <http://doi.org/10.3909/riu0679>
- Bos, Kirsten I., et al. "Pre-Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis." *Nature* 514.7523 (2014): 494-497.
- Smith, David Mark. BCG-osis following intravesical BCG treatment leading to miliary pulmonary nodules, penile granulomas and a mycotic aortic aneurysm. *BMJ Case Reports* 2016; doi:10.1136/bcr-2016-215635
- Westhovens, Ine M., et al. "Systemic BCG infection in a patient with pancytopenia and fever 9 years after intravesical BCG administration for bladder cancer." *BMJ case reports* 2016 (2016): bcr2016215599.
- Pérez-Jacoiste Asín, María Asunción et al. "Bacillus Calmette-Guérin (BCG) Infection Following Intravesical BCG Administration as Adjunctive Therapy For Bladder Cancer: Incidence, Risk Factors, and Outcome in a Single-Institution Series and Review of the Literature." *Medicine* 93.17 (2014): 236–254.
- Christensen, Anne-Sophie Halkjaer, et al. "Long-term mortality in patients with pulmonary and extrapulmonary tuberculosis: a Danish nationwide cohort study." *Clinical Epidemiology* 6 (2014): 405+. *Academic OneFile*. Web. 27 Sept. 2016.