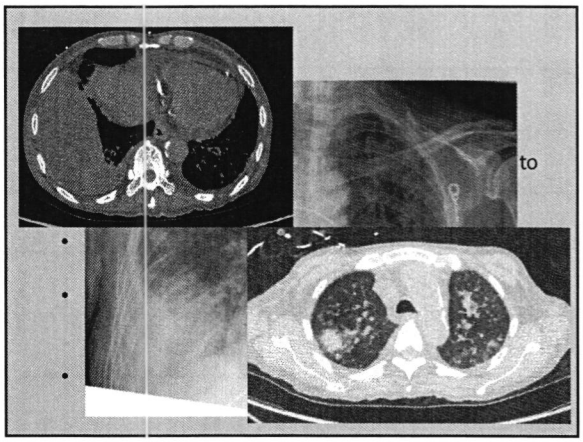
- 7 days later, admitted to outside (local) hospital
- Felt unwell, burning sensation all over body. Temp 97.8ºF. Glucose in 600s. Insulin increased and discharged.
- ID clinician spoke to inpatient hospitalist to request chest CT and thoracentesis. This was not done.

NOVEMBER 2017

- Admitted again to local hospital, with complaint of increasing weakness, intermittent diarrhea, intermittent fevers, dehydration, body aches. Temp 96.5°F. Hydrated and discharged.



to

Case 1

Q7: what TB diagnostic studies can be sent on bodily fluids, incl pleural fluid?

1. Xpert MTB/RIF and culture
2. Culture only
3. Free interferon-gamma level
4. IL-1β
5. Lipoarabinomannan ←urine/blood only
6. Adenosine de-aminase

Case 1

- **Thoracentesis: Pleural fluid culture:** AFB smear+, MTD probe positive, culture positive (drug susceptible)
- **Blood cultures:** MTB culture-positive (drug susceptible)
- **Sputum cultures:** > 9 AFB stain , MTB probe-positive, MTB culture-positive (drug susceptible)

Case 1

Interferon gamma release assay
12/16/2017

test component	normal range	patient values
TB minus NIL	≤0.34 IU/mL	0.73
MITOGEN minus NIL	--	0.65
NIL	≤ 8.00 IU/mL	0.59

Interpretation: *POSITIVE*

Case 1

- Taken to OR 12/18/2017 for decortication of right lung, bronchoscopy, and mediastinal lymph node biopsy
  - **Pathology of right pleura:** suppurative inflammation, fibrosis and non-necrotizing granulomas. AFB and GMS stain negative
  - **Stain/culture of pleural tissue:** >9 AFB, MTB culture-positive
  - **Pathology of mediastinal lymph node:** necrotizing and non-necrotizing granulomas.
  - Stain/culture of Lymph node: Stain positive for acid-fast bacilli. AFB culture positive
  - **Bronchoalevolar lavage:** Multiple black submucosal endobronchial lesions noted. +broad-based yeast. 1-9 AFB, MTB culture-positive

Case 1

- Presumed CSF involvement

CSF	Normal Range	Patient Data
nucleated cells	0 - 5 /uL	73
differential		97% lymphocytes
red blood cells	0 - 0 /uL	3
GLUCOSE	40 - 80 mg/dL	97
PROTEIN	15 - 40 mg/dL	266

- CSF AFB smear negative, culture negative
- diagnosis: disseminated TB with pulmonary and extrapulmonary involvement

Notable features of case

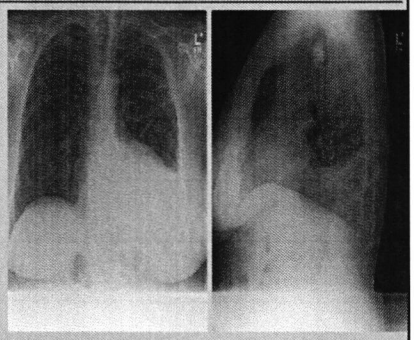
1. overlooked risk factor for infection: birth in Laos
2. multiple risk factors for progression also overlooked: diabetes, renal failure, radiographic evidence of old, untreated TB and immune suppression
3. neither active TB nor LTBI was aggressively investigated prior to transplant

⇩ ⇩

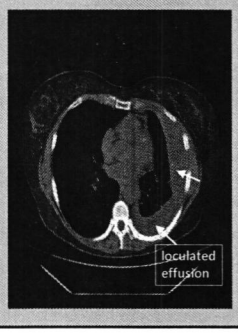
4. Diagnostic delay
5. Atypical presentation (fever was intermittent; weight loss, anorexia, body pain, persistent loculated effusion were prominent)
6. extrapulmonary and disseminated disease

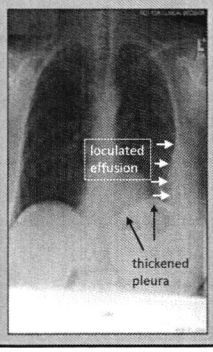
Extrapulmonary tuberculosis: clinical spectrum

pleural tuberculosis



pleural TB





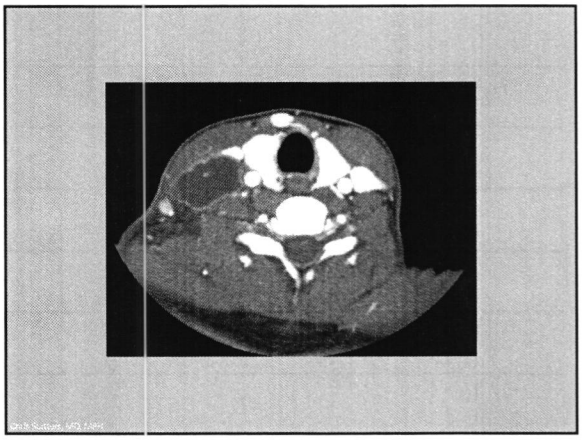
lymphadenitis

43 yo male with cervical LN swelling x 4 wks. No fever, cough.

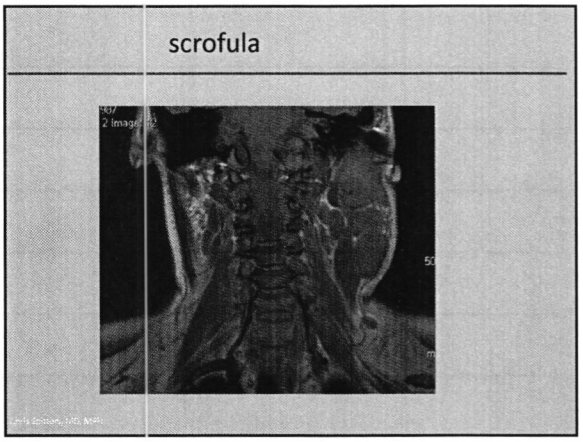
Exposure: No TB contacts. Born in Afghanistan

exam: Unilateral enlarged, non sub-
mandibular LN.

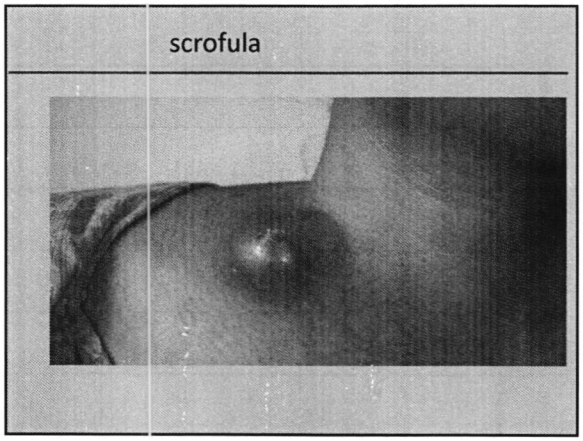
PPD 10 mm. CXR: NL



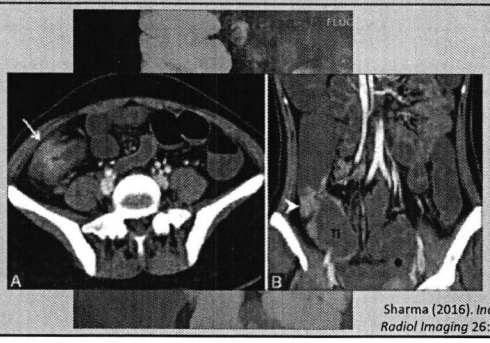
scrofula



scrofula

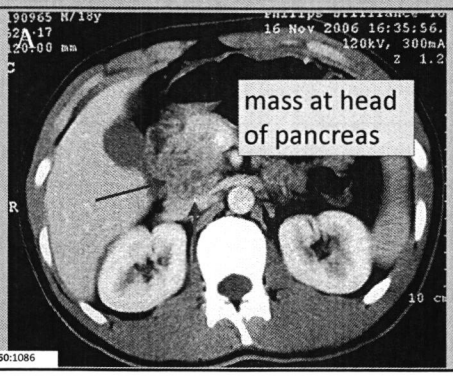


GI TB: often involves ileo-cecal junction, mimicking inflammatory bowel disease



Sharma (2016). *Indian J Radiol Imaging* 26: 161–72.

pancreatic tuberculosis

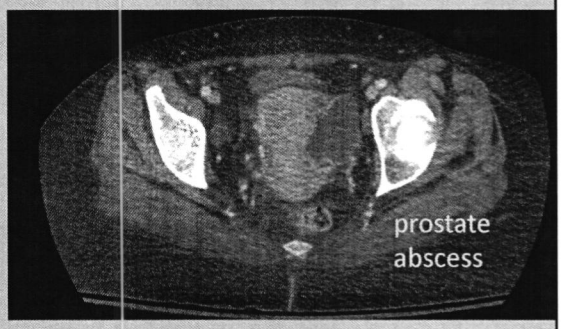


Li (2011). *Gut* **60**:1086

Genitourinary tuberculosis

credit: Chris Spitters, MD, MPH, Loren Denlinger, MD

Genitourinary tuberculosis

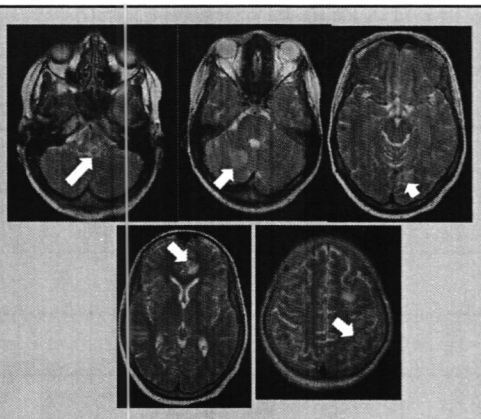


Chris Spitters, MD, MPH

spinal tuberculosis

Diskitis, osteomyelitis +/- paraspinous abscess

Chris Spitters, MD, MPH, King Country TB program, Washington state



Extrapulomary tuberculosis: diagnosis

symptoms

293

A Population-Based Survey of Tuberculosis Symptoms: How Atypical Are Atypical Presentations?

Loren G. Miller,[1,4] Steven M. Asch,[2] Emily I. Yu,[2] Laura Knowles,[3] Lillian Gelberg,[1] and Paul Davidson[3]

From the Divisions of [1]Infectious Diseases and [2]General Internal Medicine, Veterans Affairs Greater Los Angeles Healthcare System, [3]Department of Family Medicine, and [4]Division of Infectious Diseases, UCLA Medical Center, and [3]Los Angeles County Tuberculosis Control, Los Angeles County Department of Health, California

- Los Angeles county, California: April-Sept 1993
- 735 consecutive cases of confirmed tuberculosis identified prospectively
- 526 sent questionnaires → 313 completed
- predominantly male (64%), non-white (90%), foreign-born (71.4%), few HIV + (12%) , pulmonary TB (80%)
- "significant symptoms" within past 2 years:
  - cough for >2 weeks– weight loss
  - fever for >2 weeks – hemoptysis

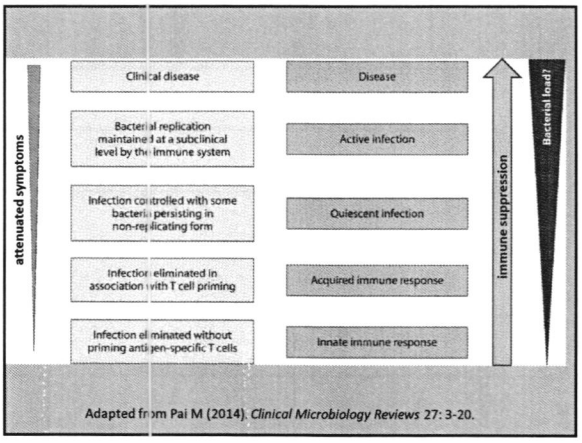
Miller LG (2000). *Clin Infect Dis* 30: 293–9

Table 2. Percentage of tuberculosis patients with specific symptoms.

	All patients (n = 313)	Pulmonary disease (n = 254)[a]	Extrapulmonary disease (n = 54)
Significant symptoms	218 (70.6)	176 (70.4)	37 (68.5)
Cough	226 (72.7)	191 (75.8)	30 (55.6)
Present for >2 w	150 (48.2)	132 (52.4)	15 (27.8)
Fever	162 (52.3)	127 (50.6)	32 (59.3)
Present for >2 w	91 (29.4)	66 (29.3)	23 (42.6)
Fatigue	185 (59.7)	147 (58.6)	35 (64.8)
Present for >2 w	127 (41.0)	105 (41.8)	20 (37.0)
Weight loss	138 (44.5)	108 (43.0)	27 (50.0)
Sweats	148 (47.9)	116 (46.0)	28 (53.9)
Present for >2 w	91 (29.4)	72 (28.6)	19 (36.5)
Anorexia	127 (40.6)	102 (40.2)	22 (40.7)
Present for >2 w	81 (25.9)	66 (26.0)	15 (27.8)
Chest pain	128 (41.0)	105 (41.5)	22 (40.7)
Present for >2 w	87 (27.9)	71 (28.1)	15 (27.8)
Diarrhea	69 (22.0)	54 (21.3)	15 (27.8)
Present for >2 w	38 (12.1)	27 (10.6)	11 (20.4)
Hemoptysis	65 (20.9)	80 (23.8)	3 (5.6)

Loren G Miller et al (2000). Clinical Infectious Diseases 30:293–9

Trait	overall No. (%)	No. (%) with significant sxs	Multivariate Analysis OR	*P*
Ethnicity				
Asian	74 (23.9)	30 (42.2)	0.17	<0.0001
Black	38 (12.3)	28 (73.7)		0.43
White	32 (10.4)	25 (78.1)		0.84
Hispanic	153 (49.5)	124 (81.0)		0.96
No Insurance	147 (51.2)	120 (82.8)	3.60 (1.65–7.83)	0.001
Homeless	26 (8.6)	23 (88.5)		0.71
Incarceration	83 (27.3)	65 (78.3)		0.74
TB diagnosed because of				
Symptoms	216 (70.1)	177 (81.9)	5.89 (2.69–12.89)	<0.0001
Screening	92 (29.9)	37 (42.0)		
Skin Test				
Positive	218 (83.5)	144 (67.0)	6.40 (1.36–30.01)	0.02
Negative	43 (16.5)	39 (92.9)		



Adapted from Pai M (2014). *Clinical Microbiology Reviews* 27: 3-20.

Diagnosis of Extra Pulmonary TB: tissue sampling

- Send respiratory samples even if chest imaging is negative.
- Bronchoscopy if cannot obtain sputum biopsy
- biopsy enlarged lymph nodes
- use CT or MRI to find extrapulmonary lesions that can serve as biopsy targets
- for pleural TB, pleural biopsy is often required
- tissue should be sent for AFB stain and culture, as well as PCR/probe testing (may need to be a reference lab)

Non-culture-based methods

Bacteria or bacterial product is detected
- *In-situ* hybridization (probe)
- DNA/RNA amplification = NAAT
  - PCR
  - rtPCR
- MALDI-TOF
- urine Lipoarabinomannan

Host response is measured
- in principle, gene expression signature

Nucleic Acid Amplification Tests (NAAT)

- **Versions**
  - Amplified MTD (GenProbe)
  - GeneXpert Mtb/RIF (Cepheid)
  - Non FDA-Approved
    - MTBDR Plus (Hain)
    - Others
- **When to Use**
  - Directly on processed (unfixed) specimen
  - No current TB rx >7 days
  - No prior TB rx within past 12 months

Sensitivity and speed of various methods of TB identification

Method	Sensitivity (# bugs required)	Speed
AFB **Smear**	10^4	Hours
Conventional **Culture**	10^3	Weeks
Radiometric/MGIT	10^{2-3}	Days
DNA Probe	10^{3-4}	Days (min?)
RNA Probe	10^{1-2}	Days (min?)
PCR (MTD) + Probe	$10^{0(?)}$	Days (hours)
PCR + DNA sequencing	$10^{0(?)}$	Days

Loren Denlinger, MD

Summary: clinical features and diagnosis

1. the key to making the diagnosis is understanding the host
2. classic symptoms (fever, cough, night sweats, weight loss, hemoptysis) may be absent or attenuate
3. diagnostic delay is common
4. certain ethnic groups may be more likely to present with extrapulmonary disease

Summary: clinical features and diagnosis

5. PPD and IGRAs have relatively poor positive predictive value for active disease
6. EPTB is typically a "paucibacillary" disease. Thus, smear and culture are less sensitive than for pulmonary TB.
7. Molecular methods are critical to making a microbiologic diagnosis. PCR is currently the most reliable non-culture-based diagnostic tool