Pulmonary Tuberculosis: Dogma Disproved

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From Laennec and Villemin...

- Laennec (1781-1826)
  - Stethoscope invention
  - Clinical-pathological correlations
  - A Treatise on the Diseases of the Chest
  - Description of caseous necrosis
- Villemin
  - Etudes sur la Tuberculosis (1868)
  - Clearly established the infectious nature of tuberculosis

...to Koch

- Discovered staining techniques for tuberculosis
- Developed culture media to grow the organism
- Demonstrated the mode of transmission
  - Approach remains a standard for implicating a microorganism as a causative agent of disease
- Recommended isolation
- Discovered tuberculin and demonstrated cell-mediated response to tuberculosis

Primary vs. reactivation TB

- Time between the initial infection and the onset of clinical disease
  - 1-5 years
- Radiographic presentation – classical teaching
  - Primary (atypical) TB: lower lobe disease, adenopathy, pleural effusions
  - Reactivation (typical) TB: upper lobe disease and cavitation

Radiographic presentation: the Dogma

- Primary (atypical) tuberculosis
  - Lower lobe disease
  - Adenopathy
  - Pleural effusions

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Radiographic presentation: the Dogma

- Reactivation (typical) tuberculosis
  - Upper lobe disease
  - Cavitation


Tuberculosis in the AIDS era

- Most common pulmonary complication of HIV worldwide
- High rate of active disease in the absence of highly active antiretroviral therapy (HAART)
  - 10% per year in patients with HIV
  - 10% per lifetime in a patient without HIV


High rate of active tuberculosis

- Loss of interferon (IFN)-γ-producing CD4+ T cells
  - Cytokine of major importance in human response against tuberculosis

Schluger NW, Renn WN. The host innate response to tuberculosis. Am J Respir Crit Care Med 1998; 157:679-691

Tuberculosis in patients with HIV

- Atypical presentation
  - Lower lobe disease
  - Lack of cavitation
  - Adenopathy
- Classical teaching
  - Atypical radiographic appearance is due to rapid progression of primary TB

Jones et al. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis 1993; 148:1202-1207

Radiographic pattern of TB depends on the stage of HIV

- CD4 counts > 354 cells/μl
  - Upper lobe disease
  - Cavitation occurs less frequently as CD4 counts decline
- CD4 counts > 200 cells/μl
  - Pleural effusions
- CD4 counts < 200 cells/μl
  - Mediastinal adenopathy

Post et al. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte counts. Tubercle Lung Dis 1995; 76:517-520

Radiographic appearance of TB predicts CD4 counts

- Apical disease
  - PPV 78% for CD4 count > 200 cells/μl
- Lower lung zone disease
  - PPV 84% for CD4 counts < 200 cells/μl
- Adenopathy
  - PPV 89% for CD4 counts < 200 cells/μl
**Dissenting opinion**

- Radiographic appearance correlates with the degree of immune impairment regardless of time since infection

Jones et al. Chest radiographic findings in patients with tuberculosis with recent or remote infection. Am J Respir Crit Care Med 1997; 155:1270-1273

**Origins of the classical dogma**

- Conclusions based in part on historical data
- Only 64% of patients thought to have had primary TB had evidence of recent tuberculin test conversion


**Molecular epidemiology**

- Allows comparison of clinical and radiographic features of TB cases without need to document seroconversion
- DNA fingerprinting
  - *M tuberculosis* DNA extraction
  - Digestion with *Pvu* II and electrophoresis
  - Hybridization by Southern blotting

**Primary vs. reactivation TB**

- Clustered cases: related in space and time
  - Identical strains recovered from 2 or more patients
  - Epidemic
  - Primary disease
- Unique cases: unrelated in space and time
  - Strains found in one person only
  - Reactivation tuberculosis


**Los Angeles County, 103 patients**

- No difference in chest radiographic findings in patients with primary vs. reactivation tuberculosis
- Atypical radiographic findings of TB in HIV are not due to recent infection

Jones et al. Chest radiographic findings in patients with tuberculosis with recent or remote infection. Am J Respir Crit Care Med, 1997; 155:1270-1273

**New York City, 456 patients**

- Time from acquisition to infection does not predict radiographic appearance
- HIV status is a predictor of radiographic appearance

Seminal papers

- Grønli-Dahl T. Tuberculosis infection in the light of tuberculin maturation. Amer J Hyg 1952; 56:139
- Poulsen A. A tuberculosis epidemic on the Faro Islands. Acta Tuberc Scand 1947; 31:58
- Frostad S. Tuberculosis incipiens: a clinical roentgenological investigation on the earliest forms of pulmonary tuberculosis with special view to its relation to the primary infection. Acta Tuberc Scand (Suppl 13), 1944

Distinction between reactivation and primary TB

- Repeated skin testing of large cohorts over the course of several years
- Gaps in historical data on the population scale
- Radiographic appearance is used instead

Choyke et al., Radiology 1983

- 64% had documented seroconversion history
- 36% classified on the basis of radiographic appearance and clinical presentation

Stead et al., Annals of Internal Medicine 1968

- 37 cases of “primary” TB
- 22 (60%) patients had documented recent tuberculin conversion
- 8 (22%) were included on the basis of radiographic appearance
  - Lymphadenopathy
  - Parenchymal disease in the lower lung zones

Stead et al., Annals of Internal Medicine 1968

- Elastic definition of primary TB
  - 65% within 9 years
  - Exclusion of any patient if “the disease involved the apical or posterior segment of the upper lobe because these are segments so commonly involved in the postprimary stage of infection.”

Stead et al., Annals of Internal Medicine 1968

- Explained reliance on radiographic appearance to distinguish primary from reactivation tuberculosis
  - “because several Scandinavian authors have reported these findings as common in primary tuberculosis and because they are rare in postprimary (so-called reinfection-type) tuberculosis.”
3,336 Norwegian students periodically tested with tuberculin over ten years

48 adult patients with proven active pulmonary tuberculosis within 12 months of the last negative tuberculin skin test

- 25 (52%) upper lung zone disease, 23 (48%) lower lung zone disease, (95% CI 0.359, 0.681)

Distribution in 28 children below 14 years of age
- 23 upper lobe disease, 6 had lower lobe disease.
- The probability of random occurrence is 18.08% at this sample size

The rates of adenopathy and pleural effusion were not reported

Documented seroconversions followed by clinical illness traced to a single source
- “Right adenitis” and pleural effusions
- Small sample size
- Many of the patients were related

Universal tuberculin testing in a population of 6,500 in Kinn, Norway between 1937 and 1944
- 130 (2%) cases of active tuberculosis following documented seroconversion
- 95 (73%) presented with adenitis

Repeated disruptions of the annual tuberculin testing program due to WWII, with frequent multi-year gaps
- 15% children
- Impoverished rural coastal population
  - Subsisting on diet of “fish, potatoes, and cereals” lacking in “meat, milk, fruit, and vegetables.”

The importance of radiographic appearance

- Reactivation tuberculosis means isolating the patient to prevent an epidemic
- Primary tuberculosis necessitates search for the source of infection
- The ability of distinguish between them is critical for preventing a major public health threat

Summary

- The classical teaching is based on faulty and incomplete epidemiologic data
- Radiographic appearance of tuberculosis
  - Depends on the patient’s immunological status
  - Not related to time from infection

Summary

- Typical appearance in immunocompetent patients
  - Apical disease
  - Cavitation

Summary

- Atypical appearance in immunocompromised patients
  - Lower lung zone disease
  - Adenopathy
  - Effusions