Radiology of Pulmonary Tuberculosis in Immune-compromised Patients: Updates

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I have no conflicts of interest to disclose with regard to the subject matter of this presentation.
TB: general facts
- epidemiology, route of infx, pathogenesis, immune....

TB vs Immune Status

TB in immune-compromised pt.
- HIV, elderly, DM, transplantation, cancer, anti-TNF, etc

TB: immune-related issues during/after tx.
- IRIS, combined lung cancer
TB: infection & disease

TB begins with Inhalation of droplet containing M. tuberculosis

Risk of transmission
- Number of infectious droplets expelled by a carrier
- Duration of exposure
- Virulence of M. tuberculosis

Alveolar space has many alveolar macrophages. This macrophage catch and eat TB bacilli.
Then, macrophages are activated and release tumor necrosis factor alpha.
Many cytokines and chemokines are released and they stimulate lymphocytes.
Activated T-cells release interferon gamma with positive feedback.
Finally, they induce intracellular killing of bacilli, macrophage apoptosis, and granuloma formation.

After inhalation

Only about 1% of the patients progress to active tuberculosis within two years of exposure.

In less than 10% of the patient, the organism remain in dormant state,

about 90%, are killed and these patients are infected but never have clinical disease for their lifetime.

Latent TB infection

- never reactivated > 90%
- reactivation TB (become infectious)

normal immunity → 5-10% in lifetime
immune compromised → risk increase↑, *7% / year in HIV(+)
Primary vs Reactivation TB

Traditionally, we thought that primary and post-primary TB are quite distinct and show different clinical, pathologic, and radiological findings.

**Primary TB**
- mediastinal LN enlargement, lower lobe, pleural effusion

**Post-primary TB**
- upper lobe lesion, cavitation, fibrosis

*By DNA finger printing study of genotypes of M. tuberculosis,* we can tell certain case is either recent primary infection or reactivation from remote latent infection.

The main factor of different radiologic findings is **not the time** from infection to clinical disease but the **integrity of immunity**

TB in immune-compromised, not in primary TB, shows atypical radiologic findings like LAP, effusion, lower lung zone distribution, and consolidation.
**Chest Radiographic Findings in Primary Pulmonary Tuberculosis: Observations from High School Outbreaks**

*TB outbreaks* occurred in 15 senior high schools in Korea.

DNA fingerprint: *clustered identical genotypes* (n=90) meaning *primary TB*.

Chest radiographs (n=58)

Normal (n=3, 5%), **Upper (n=27, 49%)**, lower (n=18, 33%), upper & lower (n=10, 18%)

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**Table 1. Abnormal Radiographic Findings in Primary Pulmonary Tuberculosis in Previously Healthy Adolescent Patients (n = 55)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small nodules (D &lt; 10 mm)</td>
<td>53</td>
<td>96%</td>
</tr>
<tr>
<td>Large nodules (10 mm ≤ D &lt; 30 mm)</td>
<td>28</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Cavity</strong></td>
<td>25</td>
<td>45%</td>
</tr>
<tr>
<td>Consolidation</td>
<td>14</td>
<td>25%</td>
</tr>
<tr>
<td>Hilar lymph node enlargement</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Mediastinal lymph node enlargement</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

This pattern is post-primary or reactivation type of radiologic findings in primary TB.

Impaired Cellular Immunity

Recently there are increasing number of people with impaired cellular immune mechanism.

*HIV infection*
Solid organ or hematopoetic stem cell *transplantation*
End-stage renal failure (uremia-associated immunodeficiency)
TNF (tumor necrosis factor) antagonist treatment for IBD, RA, psoriasis, etc.

*Immune suppression* (long-term steroid therapy)
*DM*, cancer, extreme ages (newborn, *elderly*), etc.

**Immunocompromised patients with TB**

- compared with immunocompetent patients
- respiratory symptoms
- hyponutritional state with *TST (-)*
- AFB *smear (+)* sputum
- presentation with *misdiagnosed pneumonia*
- *higher mortality rate*
- *atypical radiological findings:* a few cavities, bilateral expansive consolidation, miliary shadows, LAP, etc.

Tuberculosis in AIDS patients

Risk: 50~200 times, 25% of AIDS pts

Pathology
- extensive necrosis but few cavity
- poorly organized or no granuloma
- numerous bacilli

Radiology depends on CD4 count

> 200: typical > atypical pattern

< 200: typical < atypical pattern

↑ mediastinal and/or hilar LAP
↑ miliary dissemination
↑ extrapulmonary involvement
↓ cavitation
Case 1 - TB in HIV patient

36/M

8 months ago (MA) – travel, 6MA frequent diarrhea & general weakness, 3MA mild F/C, 2MA cough, 11kg weight loss during last 6 months

HIV(+), CD4: 11/uL, TST (-)

ill-defined patchy mass-like opacity in right suprahilar area, right paratracheal and hilar bulging shadow

CT scan shows, patchy consolidation and GGO, LN enlargement with necrotic low-attenuation.

Smear/culture (+) for MTB on sputum & bronchial aspirates
Case 2 - TB in HIV patient

31/M with minimal dry cough for 1 month

HIV (+), CD4: 460/µL, TST (-)

irregular patchy and nodular opacities in RULZ.
CT scan shows aggregation of several irregular centriflobular nodules

AFB smear (-) & culture (+) for MTB on sputum exam.
Miliary tuberculosis: a comparison of CT findings in HIV-seropositive and HIV-seronegative patients

1J Y KIM, MD, 1Y J JEONG, 1K-I KIM, MD, 1I S LEE, MD, 2H K PARK, MD, 3Y D KIM, MD and 3H SEOK I, MD

Usual findings of miliary TB: disseminated micronodules & GGO

Miliary TB in HIV (+)

more interlobular septal thickening, necrotic lymph nodes, extrathoracic involvement
less large nodules

Brit J Radiol 2010;83:206–211

Case 3 - TB in HIV patient

44 / M

poor oral intake & G/W 3m

intermittent F/C, cough 1m

HIV (+), CD4: 8/uL

Numerous disseminated nodules, ill-defined patchy GGO, mediastinal widening and also we can see irregular air-density within mediastinal shadow on chest PA.
Case 3 - TB in HIV patient

Pathologic DIAGNOSIS: Tuberculosis with necrotic abscess and fistula formation, esophagus. Numerous acid fast bacilli are identified in the all layers of esophagus on Ziehl-Neelsen stain.

S/P esophagectomy

Esophageal rupture and large fistula with irregular air cavity within mediastinal LAP

numerous tiny miliary nodules, ill-defined GGO, extensive interlobular septal line thickening, extensive mediastinal LN enlargement with irregular air cavities, and large fistula between esophagus and mediastinal LN, patchy consolidation with small air cavities
TB in solid organ transplantation

20–74 times of general population
higher frequency in lung recipients
2/3 occur in 1st post-transplant yr (median: 9Ms)
reactivation of old TB foci
MTb from donated organ (renal, lung, liver transplantation) < 5%


Radiologic findings
not characteristic & wide spectrum
nodules, consolidation, fibrocavitary changes in UL, enlargement of mediastinal LN, & pleural effusion

The deeper immunosuppression, the more
consolidation (caseous Pn) with necrosis
miliary dissemination
mediastinal LAP

Pol J Radiol 2012;77(3):64-70
Case 4 - TB in solid organ transplantation

46/M with HBV & alcoholic LC, Pre-operation w/u for LT, Dec 2008

fibrotic scar, linear atelectasis, minimal focal bronchiectasis, several small irregular nodular opacities with partial calcification in BULZ.

1970 1 year medication for TB

2009 Feb 11, Living Donor Liver Transplantation

*Immune Suppression*

with Myconol & Tacrolimus (T-cell inhibitor)

2009 Apr 10 Chest Pain
2009 Apr 22 cough & dyspnea
2009 May 1 night fever, aggravation of other symptoms
2009 May 2 ER visit

Mar 2009
May 2, 2009

nearly same as preoperation chest PA except right pleural effusion probably postoperation change on Mar 2009

doodious air-space consolidation, irregular mass-like and nodular opacities, and bilateral pleural effusion on May 2009
Case 4 - TB in solid organ transplantation

mass-like consolidations
necrotic low-densities
small air cavities
several small irregular nodules
mainly in the same areas of fibrotic and nodular lesions on pre-operation CT scan

→ this may be interpreted as reactivation of latent TB in BUL.

sputum, Smear/Culture (+) for MTB
Case 5 - TB in solid organ transplantation

37/M, Kidney Transplantation 11 years ago

*long-term steroid & cytotoxic immune suppression for chronic rejection, no chest symptoms*

RUL consolidation with irregular air-cavities and multifocal ill-defined patchy and nodular opacities, mainly in both upper lung zones on chest PA. Extensive consolidation, necrosis, cavities, and multiple irregular nodules and lobular consolidations, irregular centrilobular nodules on CT.

*sputum: S/C (+) for MTB*
Tuberculosis in DM

Diabetic patients have immune dysfunctions, esp. cellular immunity is decreased and the adherence of mycobacterium to diabetic cells increase. DM is a risk factor of getting TB about 3-11 times.

lower lung field involvement
large consolidation with cavities
extensive local spread
higher prevalence of smear (+)
(cavitary lesions with a large population of bacilli)

Non-segmental distribution & multiple small cavities within lesions


J Ikezoe, et al. AJR 1992;159:1175-1179
Tuberculosis in DM

Table 3: Effect of diabetes mellitus (DM) on radiological appearance of tuberculosis (TB)

<table>
<thead>
<tr>
<th>Country, year</th>
<th>No. patients with TB</th>
<th>Radiological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM</td>
<td>No DM</td>
</tr>
<tr>
<td>USA, 1974</td>
<td>20</td>
<td>182</td>
</tr>
<tr>
<td>South Africa, 1980</td>
<td>9</td>
<td>427</td>
</tr>
<tr>
<td>United Kingdom, 1983</td>
<td>43</td>
<td>31</td>
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<tr>
<td>Japan, 1992</td>
<td>39</td>
<td>71</td>
</tr>
<tr>
<td>USA, 1992</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Turkey, 1994</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Saudi Arabia, 1997</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Turkey, 2001</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Mexico, 2000–2001</td>
<td>192</td>
<td>130</td>
</tr>
<tr>
<td>Saudi Arabia, 2003</td>
<td>187</td>
<td>505</td>
</tr>
<tr>
<td>Malaysia, 2005</td>
<td>230</td>
<td>1226</td>
</tr>
<tr>
<td>Taiwan, 2005</td>
<td>99</td>
<td>362</td>
</tr>
<tr>
<td>Texas, 2007</td>
<td>401</td>
<td>1040</td>
</tr>
<tr>
<td>Taiwan, 2009</td>
<td>74</td>
<td>143</td>
</tr>
</tbody>
</table>

n.a, not available; NS, not significant.

Recent several reports tend to admit more lower lobe involvement and also more cavitations in DM-TB.
Case 6 - TB in DM

61/M with cough/sputum 3 wks, chronic alcoholics & uncontrolled DM for more than 10yrs

FBS 325 mg/dL, HbA1c 10.9%, sputum: S/C (+) for MTB

Chest PA shows ill-defined patchy consolidation in RLL and irregular nodular opacities in RUL.

CT images show extensive consolidation in RLL, necrotic low densities, small cavities, and also we can see several foci of clustered centrilobular micronodules in peripheral portion.
**Case 7 - TB in DM**

44/M with mild fever 1 week, poor controlled DM for 5 months

Sputum smear (-) & culture (+) for MTB

Chest PA shows multifocal ill-defined patchy and nodular opacities in RUL apex and BLLZ.

We can see lobular consolidation with small air cavity and several satellite centriflobular nodules, nonspecific patchy and mass-like consolidation RML and LLL basal lung.
Tumor Necrosis Factor α  TB: anti-TNF therapy

Proinflammatory Cytokine: acute phase reaction of systemic inflammation

Primary role
regulation of immune cells & endogenous pyrogen
fever, apoptotic cell death, sepsis, cachexia, inflammation, inhibit tumorigenesis & viral replication

granuloma formation → sequester M. tbc & prevent dissemination

Dysregulation of TNF in autoimmune disease
Alzheimer’s ds, cancer, major depression, RA, psoriasis, ankylosing spondylitis, inflammatory bowel ds (Crohn’s ds), refractory asthma, etc.

Sometimes treated by TNF inhibitor
Monoclonal antibody
Infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia)
Circulating receptor fusion protein
Etanercept (Enbrel)

no infliximab
Well-formed granulomas with negligible overt necrosis

with infliximab
Prominent interstitial fibrosis, lymphoid inflammation, without granulomas

Increase reactivation of tuberculosis after Tx with infliximab for a median of 12 weeks

Extrapulmonary tuberculosis: 56%
Disseminated disease: 24%

NEJM 2001;345:1098-1104
Case 8 - TB with anti-TNF therapy

26/F with cough, sputum, mild fever & chill for 2 weeks

2006 Crohn’s disease  2009 infliximab therapy

EBUS biopsy specimen smear (-) & culture (+) for MTB

Chest PA shows newly appeared patchy consolidation and right pleural effusion.

CT shows Consolidation, GGO, and extensive interstitial infiltration with septal line thickening in RML and RLL, right pleural effusion and multiple LN enlargement, primary pattern of TB.
Tuberculosis in Elderly

↑ elderly population [more TB exposure]

↓ cellular immune function & inflam response
high rate of co-existing disease (DM, Ca)
→ insidious & non-specific clinical presentation
→ delay in Dx & Tx → ↑ morbidity & mortality

more common extrapulm. & multi-organ TB

Case 9 - TB in elderly

84/F with cough & GW for 2 wks
no fever, chill, or sputum, no underlying disease

sputum s/c (+/+ ) for MTB

Chest PA shows extensive consolidation, subtle cavities, irregular nodular opacities, small amount of pleural effusion.
Left lung shows extensive consolidation, heterogenous low densities, several small air cavities on CT scan. We can see multiple small irregular centrilobular nodules and lobular consolidation in RUL.
IRIS in AIDS Patients

Gradual ART (anti-retroviral therapy)-induced immune-recovery in AIDS patient

Dys-regulated restoration of immune function & over-reaction to pathogen
- unwanted inflammatory response during tx
- Trigger presentation of subclinical ds. [unmasking]
- ↑ rapidity & intensity of clinical presentation

Case 10 – IRIS after anti-retroviral therapy

31/M with AIDS
high burden of HIV RNA $> 10^6$ copies/mL and low level of CD4: 35/μL

CT scan shows multiple LN enlargement in right lower neck and right paratracheal area, confirmed as TB and AIDS co-infection.
Anti-TB and anti-retroviral therapy begin.

Case 10 – IRIS after anti-retroviral therapy

3 months after ART (anti-retroviral therapy)

*HIV RNA:* $> 10^6$ copies/mL $\rightarrow$ 433 copies/mL

*CD4:* 35 cells/μL $\rightarrow$ 142 cells/μL

CT scan shows increased size and necrotic low-density in right lower neck and mediastinal lymphadenopathy.

This is transient aggravation of LAP during anti-TB medication and improvement of immune status in AIDS patient.
IRIS in Non-AIDS Patients

Paradoxical response of TB

Enhancement of immune reaction: shift in T helper response
- anti-inflammatory (Th2) vs pro-inflammatory T cells (Th1 & Th17)
- uncontrolled inflammatory response

Host’s delayed hypersensitivity response: to tubercle protein released from destroyed bacilli after tx

Singh N. Lancet Infect Dis 2007;7:395-401

2nd week ~ 9th months (average 3rd M) after anti-TB
- 6~30% according to clinical form: extra-pulmonary & disseminated TB > pulmonary TB

¾ expanding pre-existing lesion in same location
¼ new lesion in different location


Recurrent fever
- pleural effusion

Lymph node enlargement

New parenchymal lesions
- peripheral well- / ill-defined nodules, mass with central low-att.

CNS: brain parenchymal, extradural/intramedullary tuberculoma

Int J Tuberc Lung Dis 2007;11:1290-95
Radiology 2002;224:493-502
Case 11 – IRIS in non-AIDS patient

32/M with f/c, left pleuritic chest pain for 1 week

Pleural tapping → lympho-dominant exudate, ADA 76 → s/c (-/+ for MTB

Nov 2008 ~ Jul 2009: anti-TB medication

4 months after medication, left pleural effusion nearly disappeared, but we can see new mass-like opacity in LLLZ.

Continue TB medication → decreased mass-like opacity in LLLZ.
Lung Cancer & TB

In patients with TB, [on chest radiographs]
  average delay in lung cancer Dx: 6~9 months
  missed new lesion masked by stable TB
  misinterpretation of new lesions as aggravation of TB

TB & lung cancer: interact in both directions
  as one of cause & effect (scar cancer)
  as reactivation of TB by cancer
  as coincidental occurrence

Signs of coexisting lung cancer

[atypical course of TB during tx.]
  new lesion or progression of lesion
  segmental or lobar atelectasis
  unilateral hilar enlargement
  irregular large nodule (>3cm)
  thick-walled cavity
  homogenous infiltration without air-bronchogram

→ enhanced chest CT, bronchoscopy & biopsy

Case 12 – Lung cancer in TB

58/M, mild fever, cough, night sweating for 2 months, dyspnea for 10 days

Chest PA shows irregular patchy and nodular opacities in BULZ and left parahilar areas.

On CT images, we can see multiple well-defined irregular nodules, peribronchial infiltration with bronchial lumen narrowing in LUL and left hilar LN enlargement, suggesting active tuberculosis.

**Bronchoscopy:** mucosal hyperemia, swelling, whitish necrotic materials in LUL bronchus → **active endobronchial TB**

**sputum S/C (+) for MTB**

Mar 14
Case 12 – Lung cancer in TB

anti-TB medication: Mar ~ Sep

f/u chest PA on 10th October shows decreased patchy and nodular opacities in lung fields, but residual and prominent left hilar opacity. Eventually, we can see LUL collapse on f/u chest PA 7th November.
Nov 21

CT images show total occlusion of LUL bronchus by ill-defined mass, mixed with peripheral collage, left hilar and mediastinal LNs, suggesting lung cancer

Bronchoscopy shows total occlusion of the LUL bronchus with a fungating mass, finally confirmed as squamous cell carcinoma
Summary

• What is the role of radiology in Tuberculosis?
• **Increasing threat** of HIV infection, immune compromised conditions, increasing number of old people.
• **Atypical manifestation** that we have to know and be familiar with high index of suspicion and **active participation** of radiologist in diagnostic procedure, sometimes with biopsy is necessary.
References and Suggested Readings

Pulmonary tuberculosis: up-to-date imaging and management. AJR 2008;191:834-844.
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