
Prof. F. Rasmussen

Lets start !

Case 1

- 27 years old man with severe Rheumatoid arthritis comes to your clinic with a complain of tiredness, dry cough, weight loss and night sweat.
- What will you do ?
- Bonus information: He started etanercept 2 month ago.

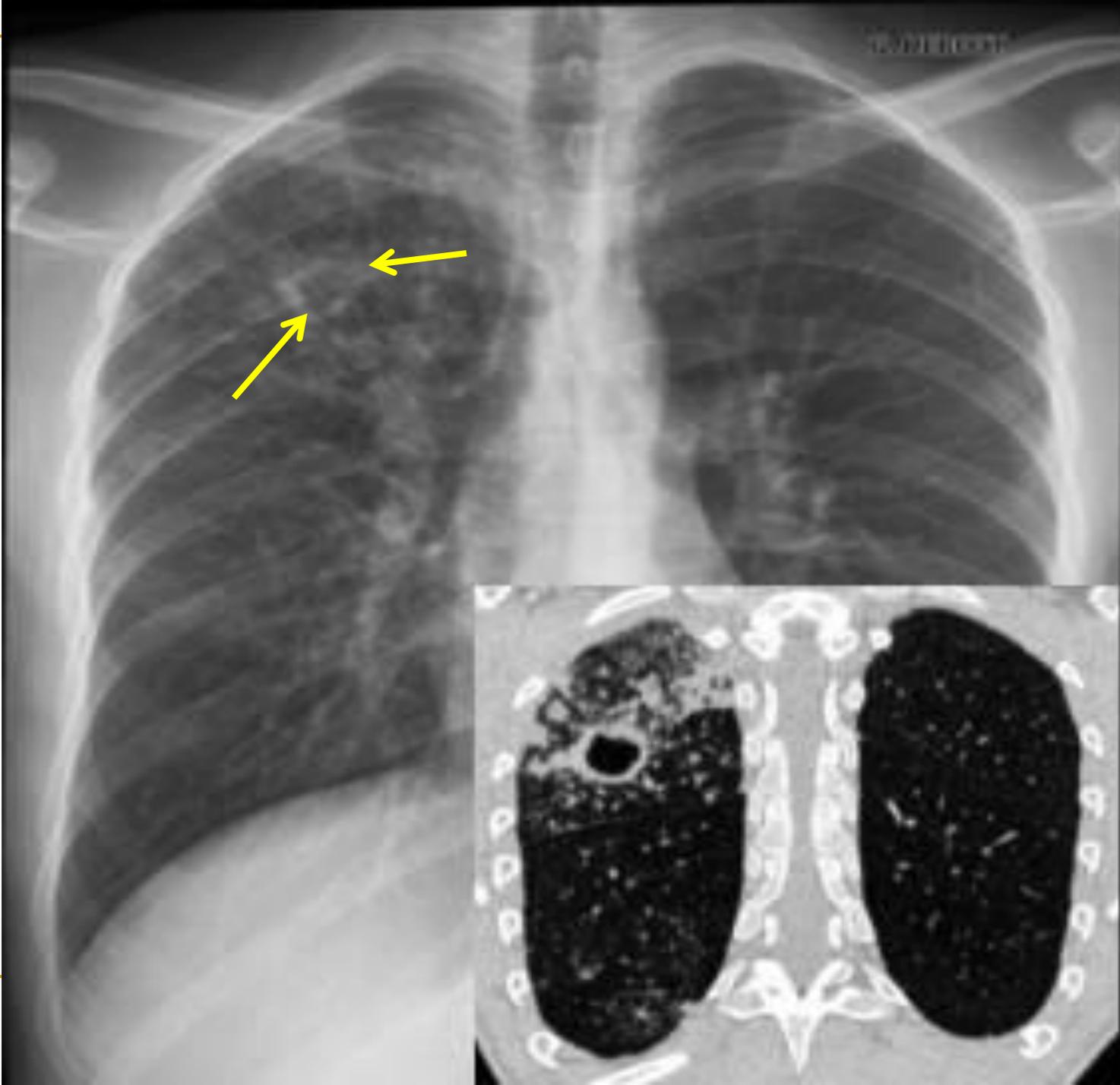
Case 1

- Rheumatoid arthritis and TNF alfa treatment !!
- Think infection !

Case 1 But...

What will you have to do ?

- Make a diagnosis !!
- Anamnesis
 - More information: How long, fever ?, Is weight loss real, sweating, haemoptysis, medicine ??
 - Smoking history
- Tests (starters !!)
 - Blood tests
 - X-Ray
 - Probably sputum culture



Symptoms: weight loss, fever,
haemoptysis

X-Ray: Infiltration (caverna)

TB

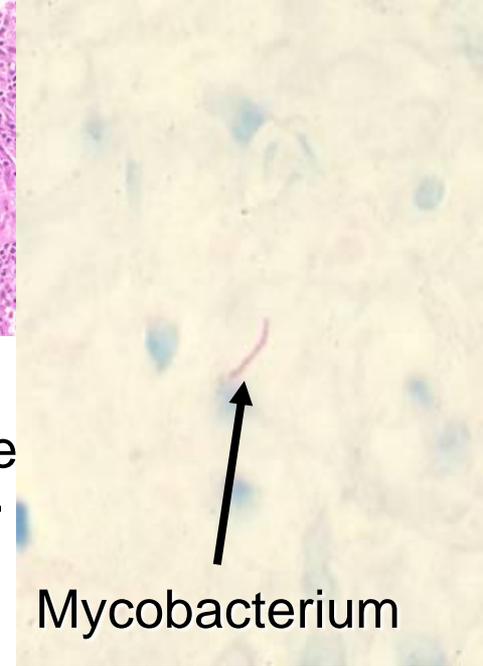
Granuloma



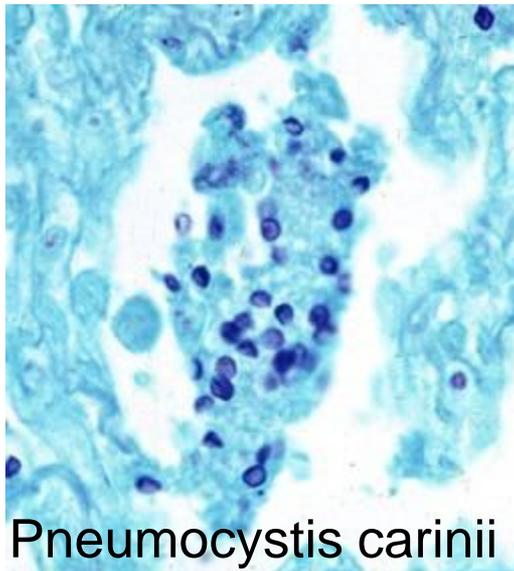
- Case 1 (most likely)

- Secondary tuberculosis infection

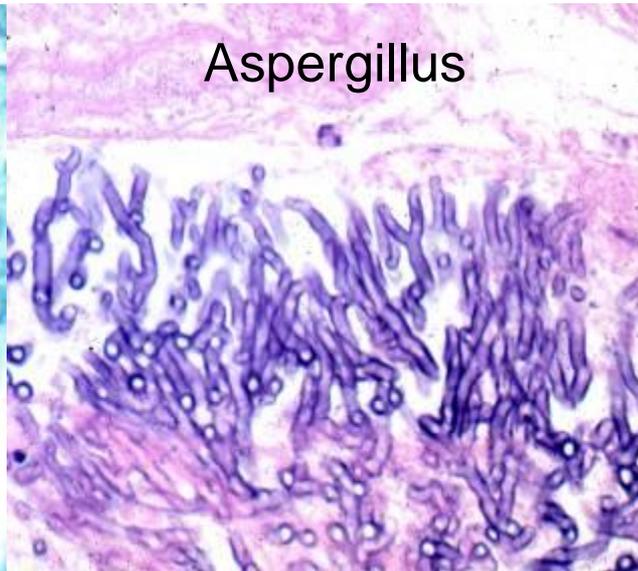
- (mostly through reactivation) in a previously sensitized individual due to a newly started immunosuppression.
- Also think in this case:
 - “regular” pneumonia
 - Other opportunistic pneumonias
 - Aspergillus, Pneumocystis carinii, Cytomegalovirus



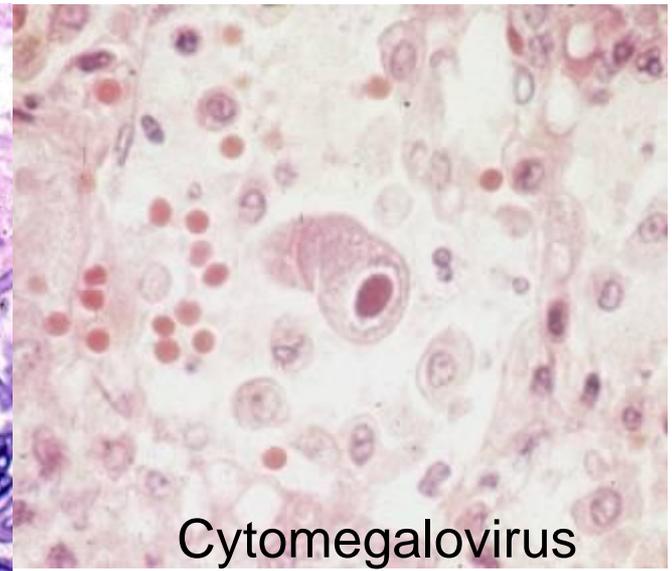
Mycobacterium



Pneumocystis carinii



Aspergillus



Cytomegalovirus

Mohamed, Sahro Abdisalaan

30.08.06 time 09.49

Mohamed, Sahro Abdisalaan

The Pt. came from Somalia 4 yrs ago.

Pt. is primary sent by her doctor to the audiological department in the hospital because of impaired hearing for evaluation.

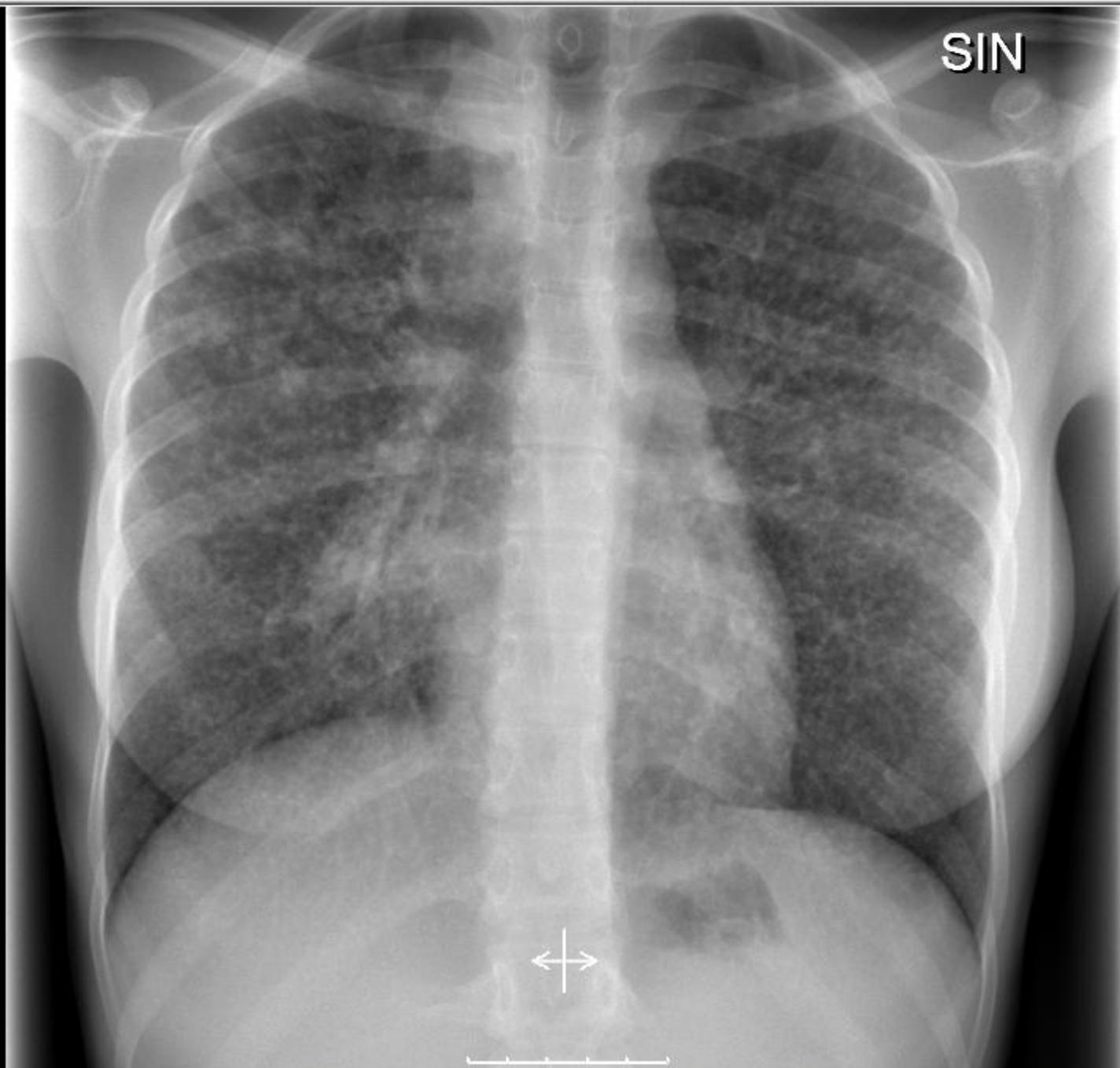
Medical history : The woman has no tinnitus, feels swell and does not want this evaluation. Operation in Mogadishu as 4 yrs old, it's not clear for what and why.

Objective Findings (audiologist wrote): clear cut decreased hearing on left side, normal right side. Do not think a hearing apparatus will help. That discrimination is perfect and due to a mastoidectomy, I think must likely it was present already due to the cochlear "procedure" in Mogadishu.

The patient has cough and some temperature, we send her for evaluation to the lung department.

-
- At lung department: 2 month ago start with cough and temp 37-38.
 - Also some dyspnea. Nausea for some time and weight loss from 44kg to 38kg in aprox 2month.
 - Temp. 36,8. BT 85/60. Puls 116. SAT 96 %. weight 38 kg. Other than thin looks OK.
 - STp: normal; STc: normal

 - Supplement
 - In her school last year 2 TB cases but not the same class.
 - Abnormal Blood test: CRP 6.2, s-albumin 32 g/l, LDH 530, fibrinogen 16,6, IgA 8.72.
-

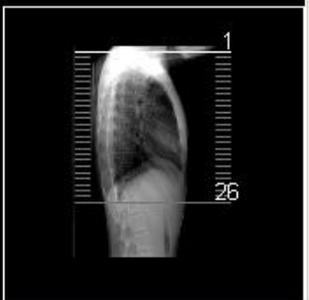
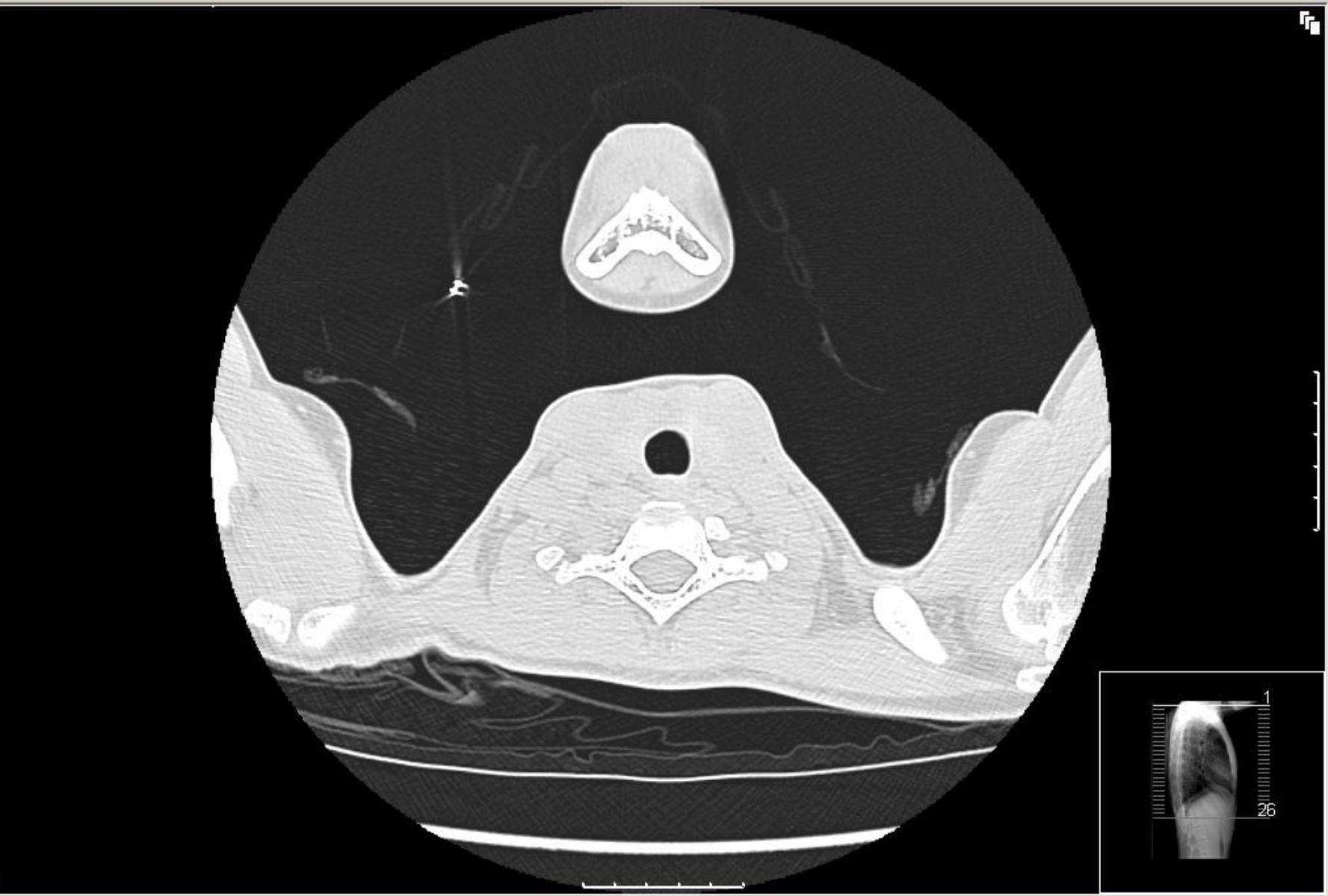


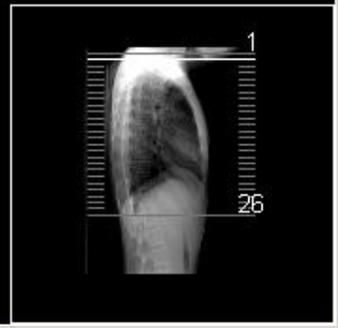
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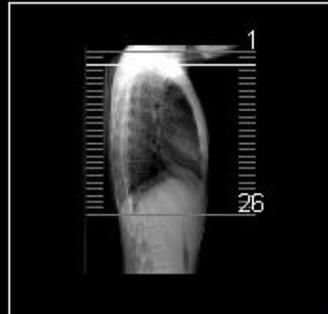
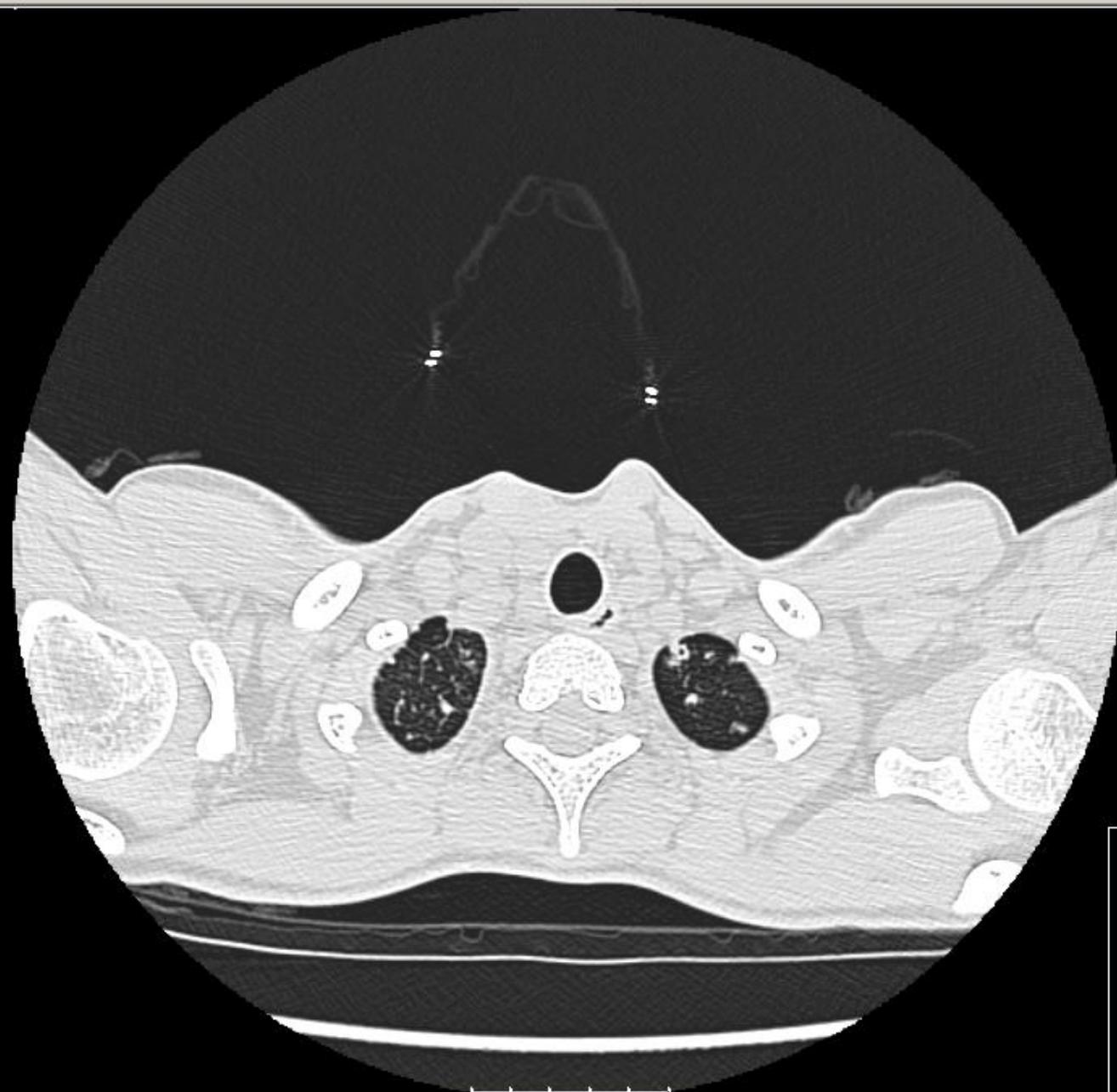


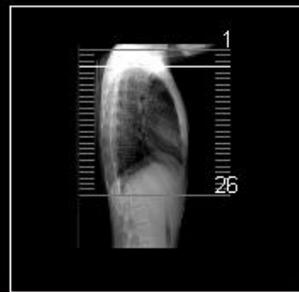
X-Ray

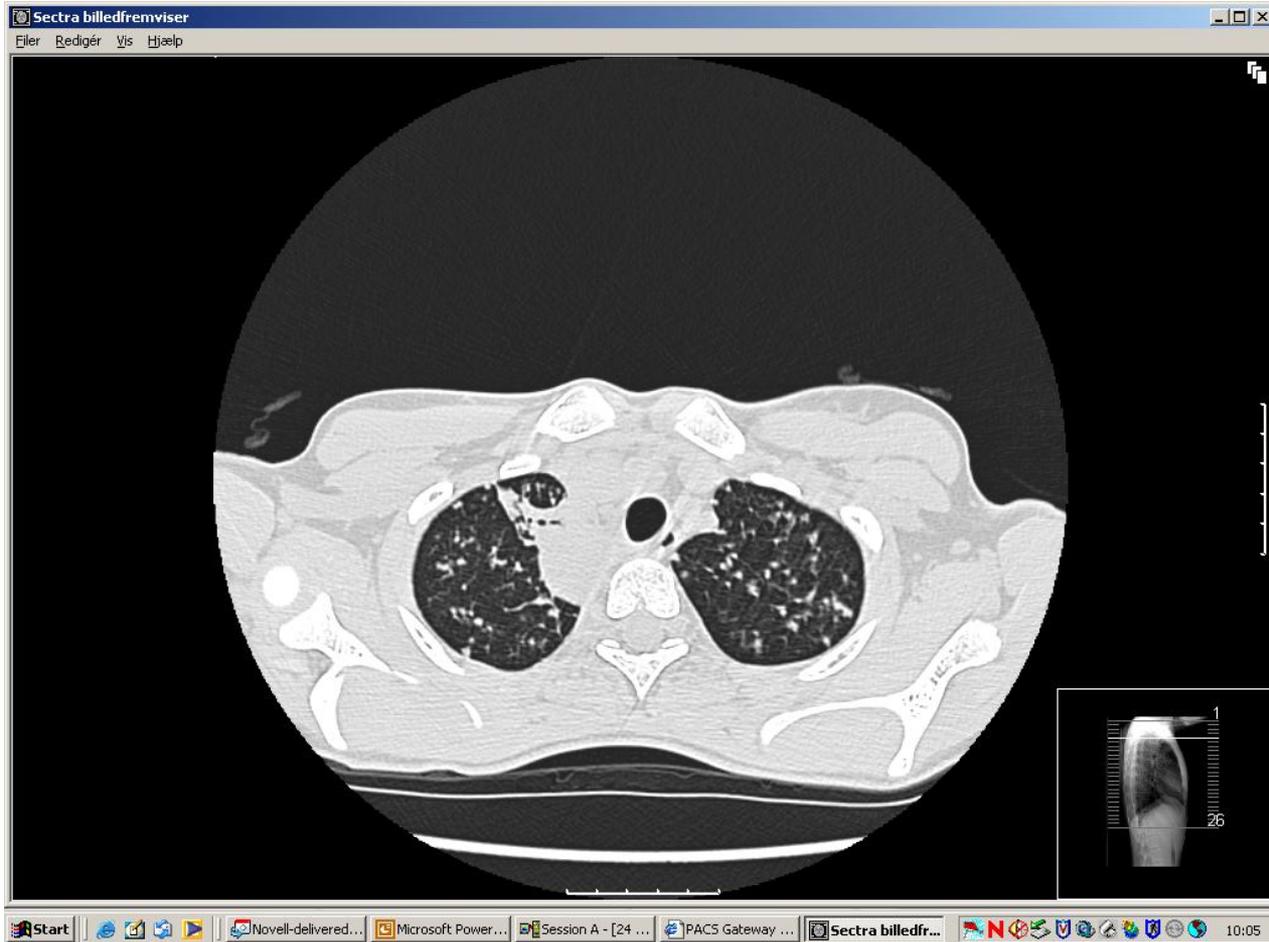
- RD:
 - Infiltratio pulmonis bilateralis
 - Ectasia mediastini superioris dx. obs. pro
 - Miliar tuberkulose obs. pro
-

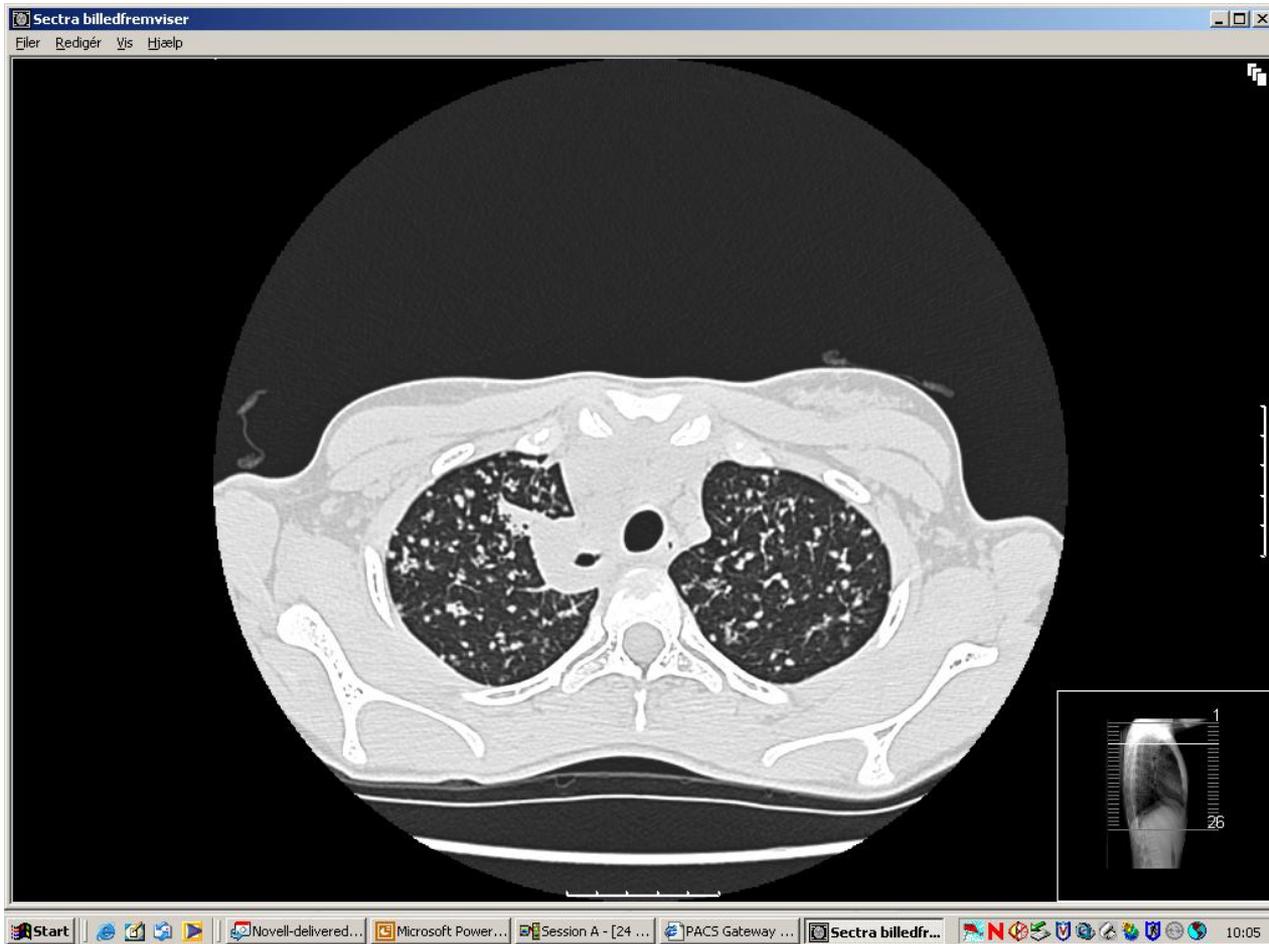


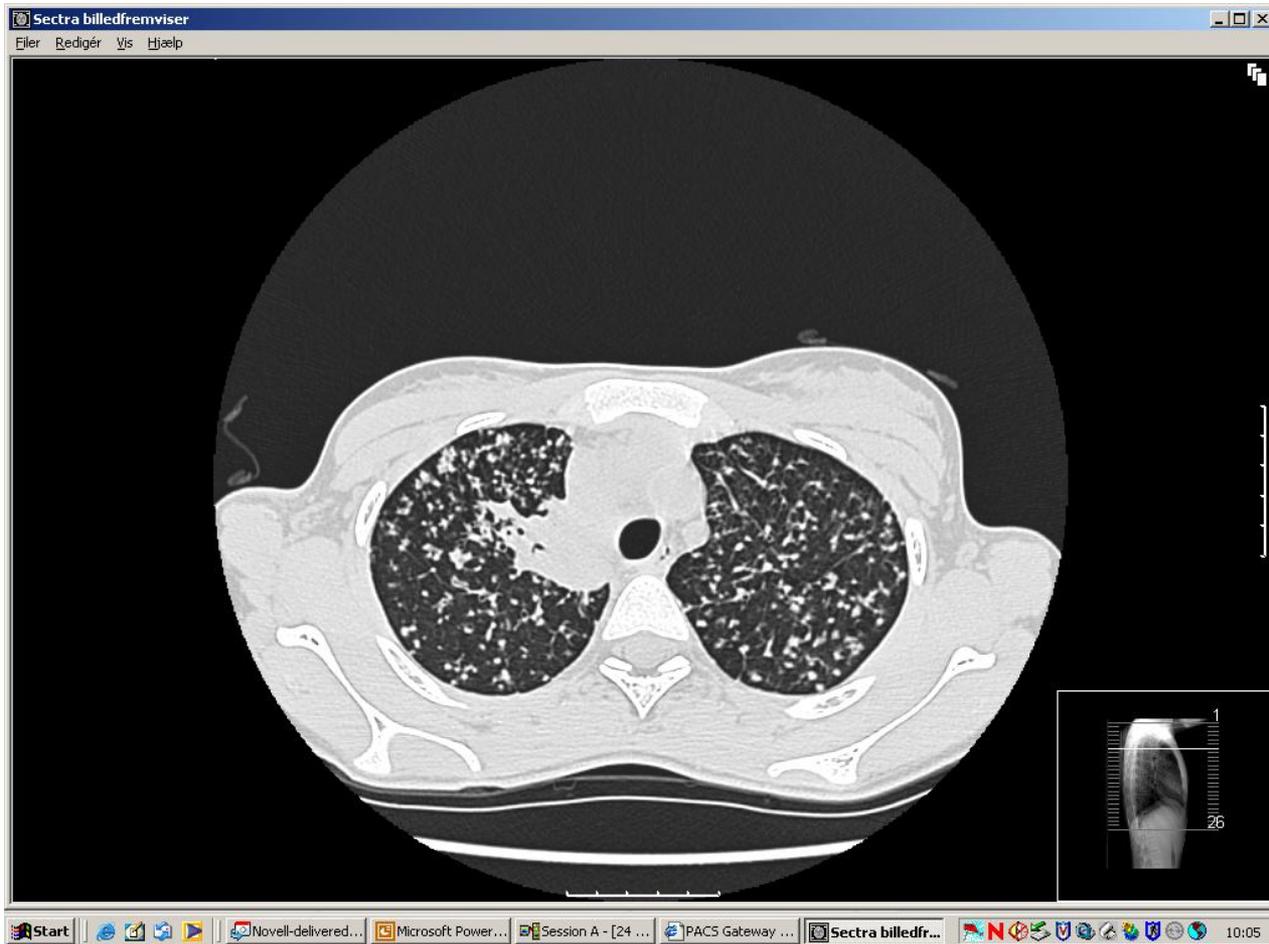


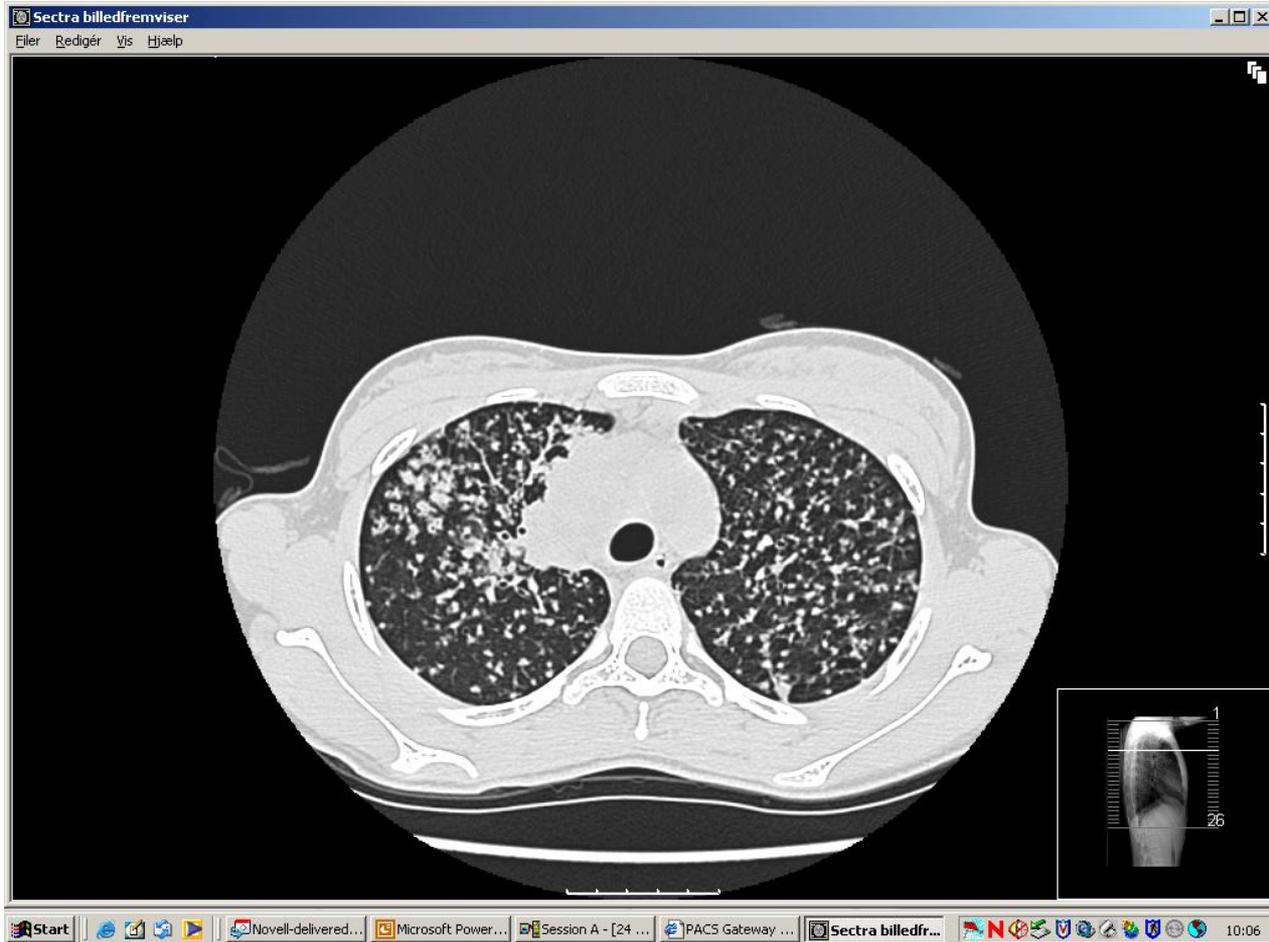




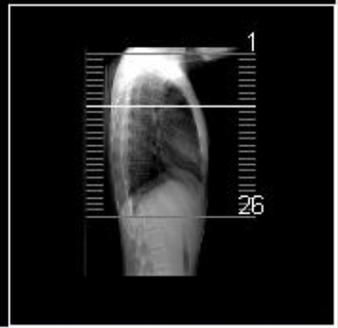
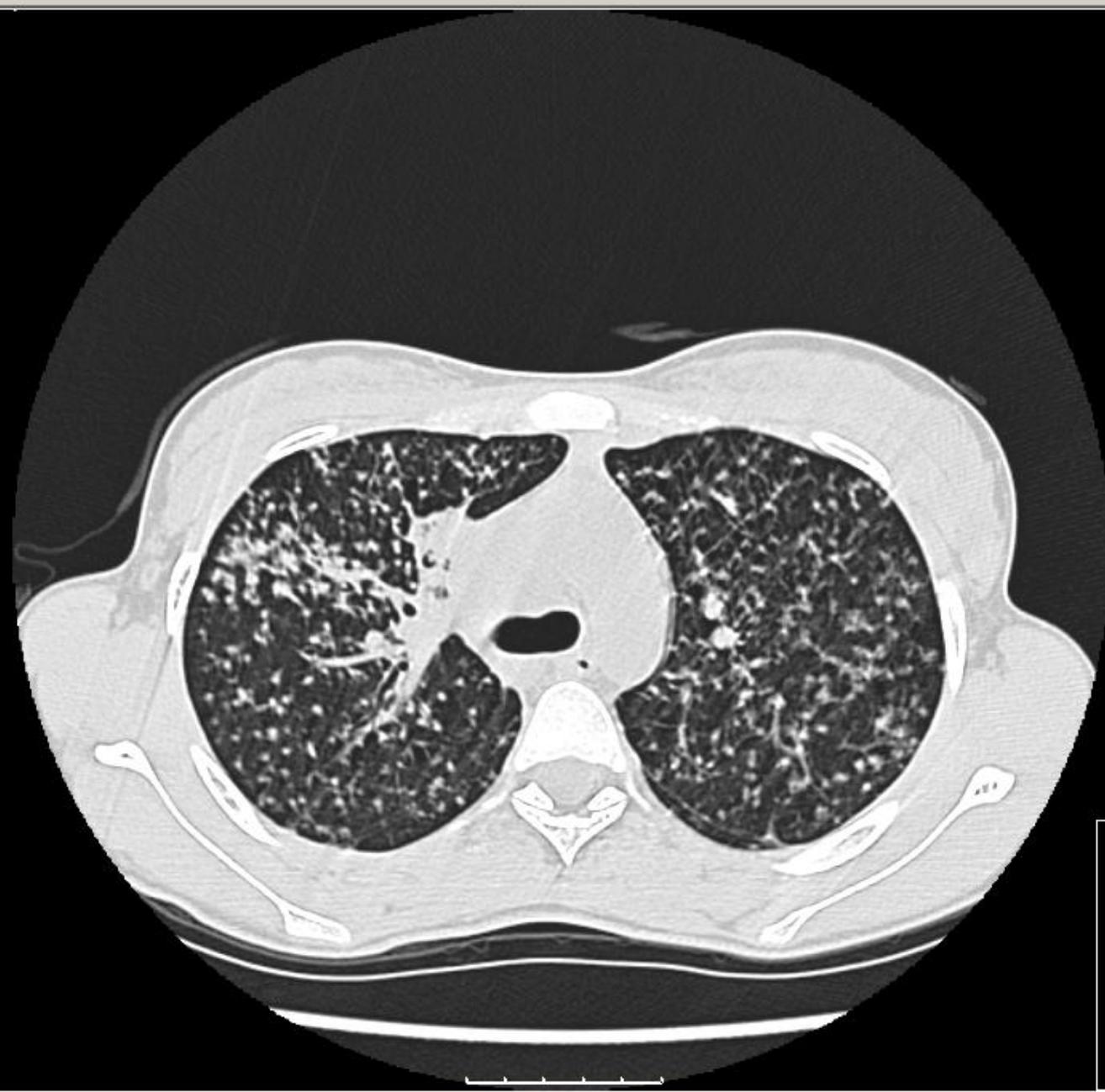


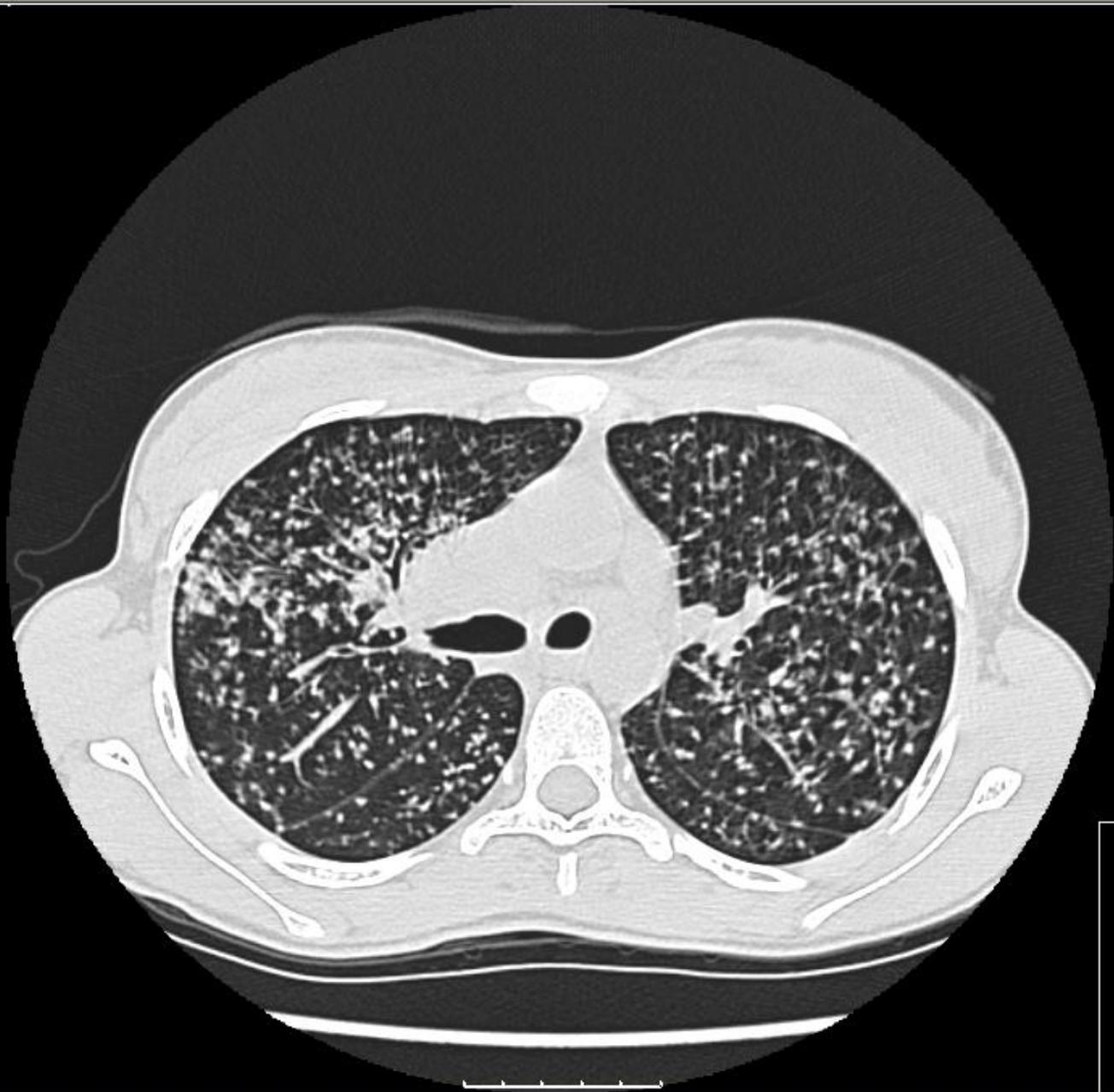


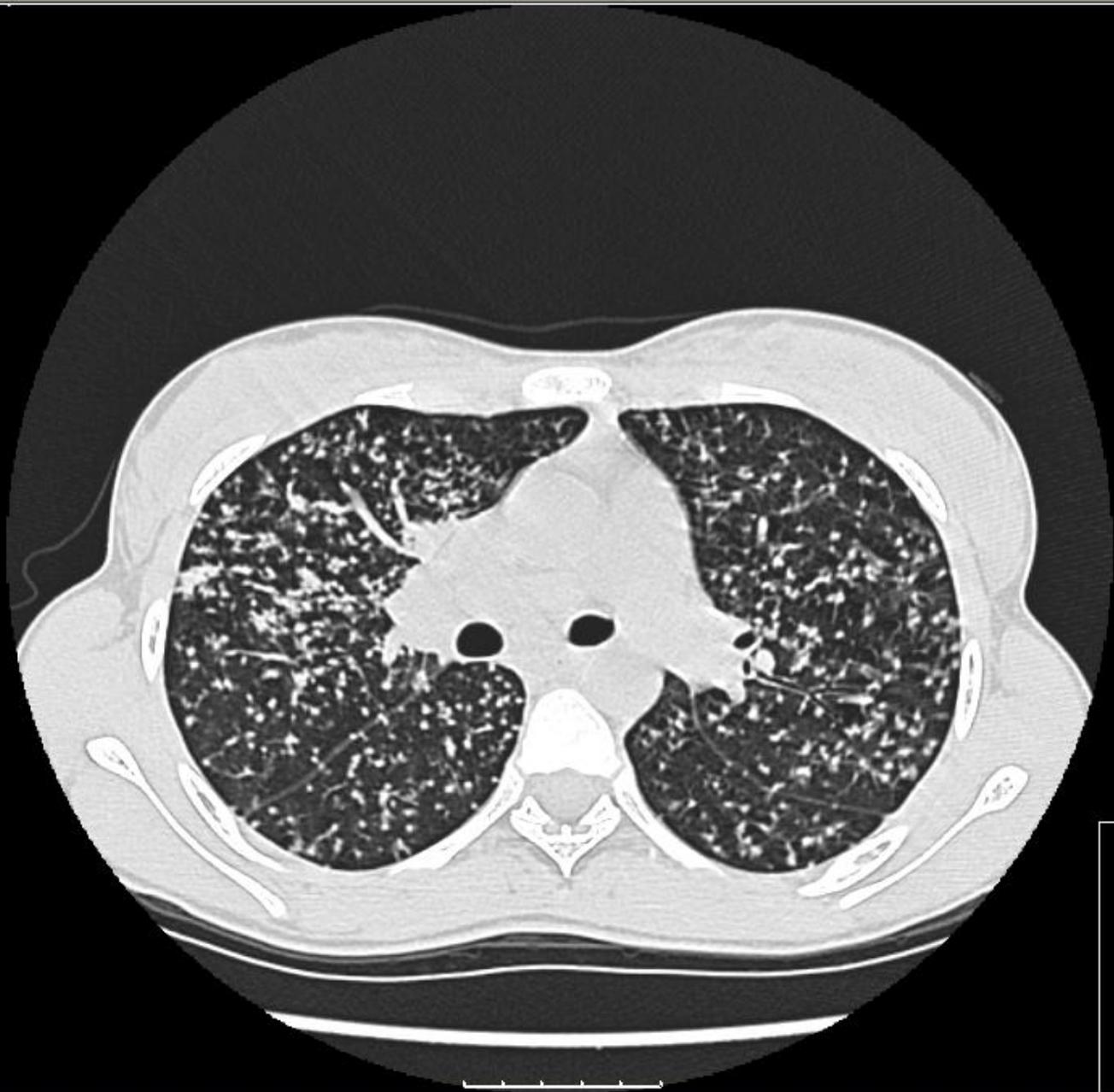


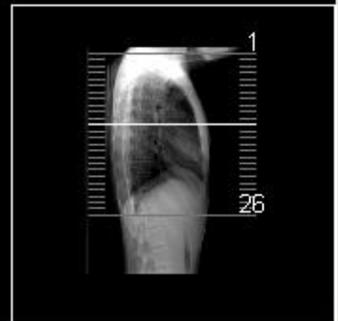
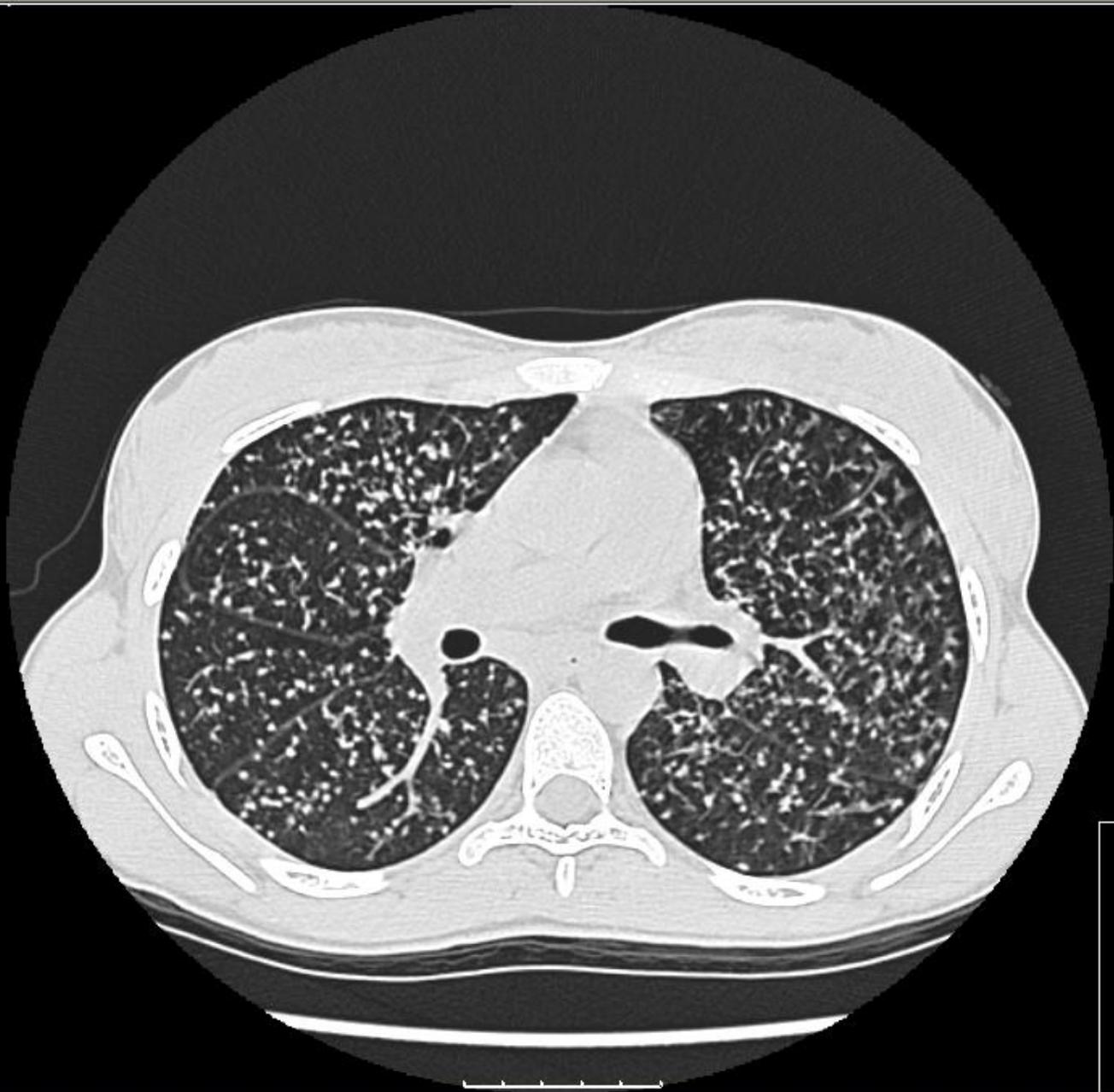


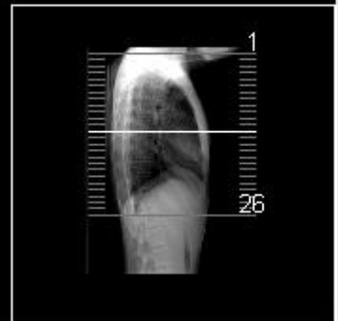
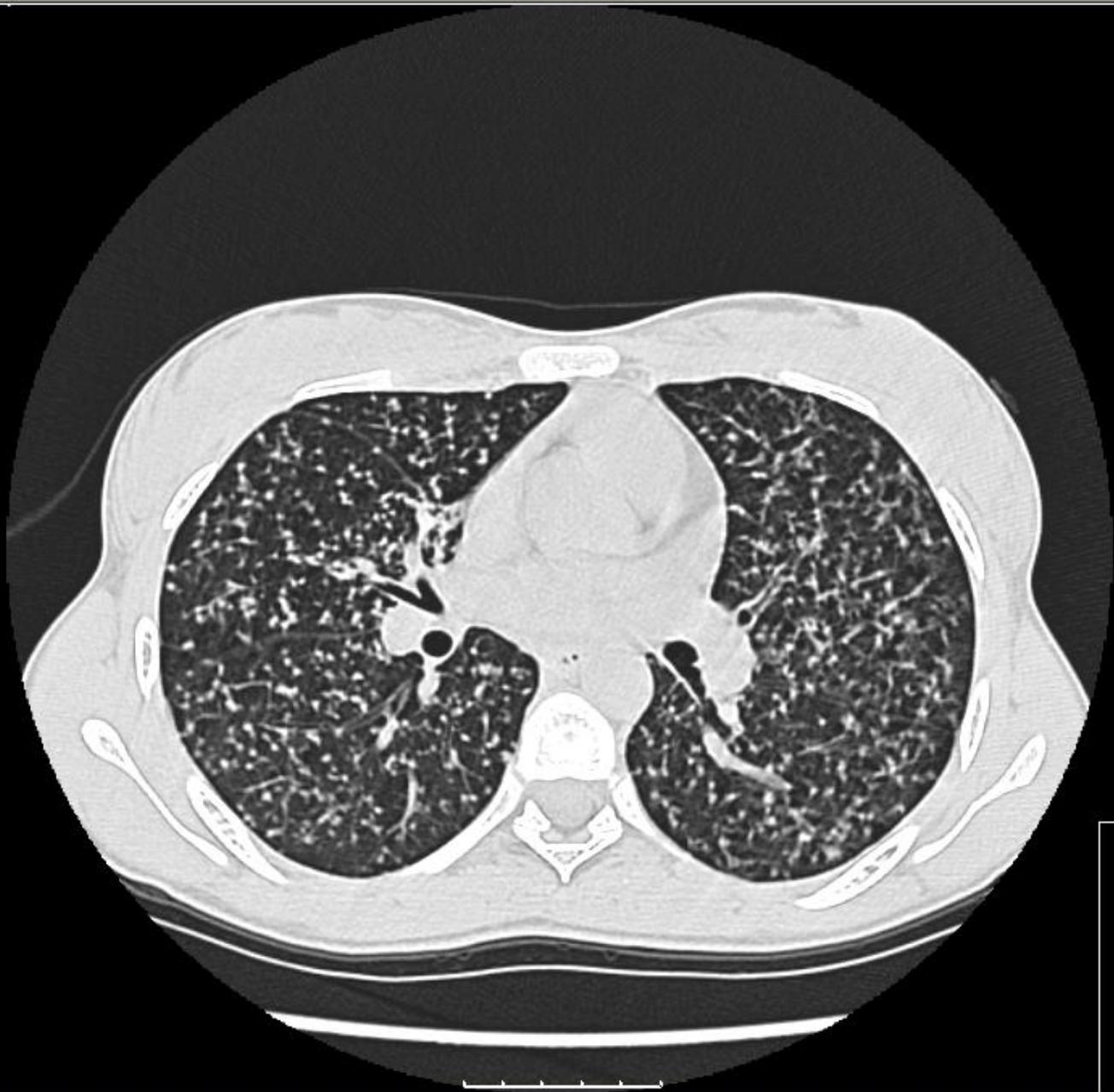


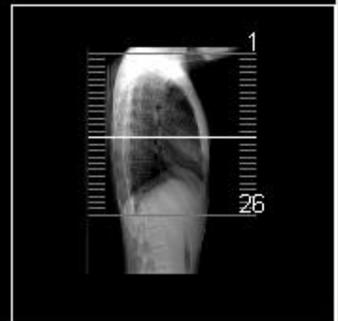
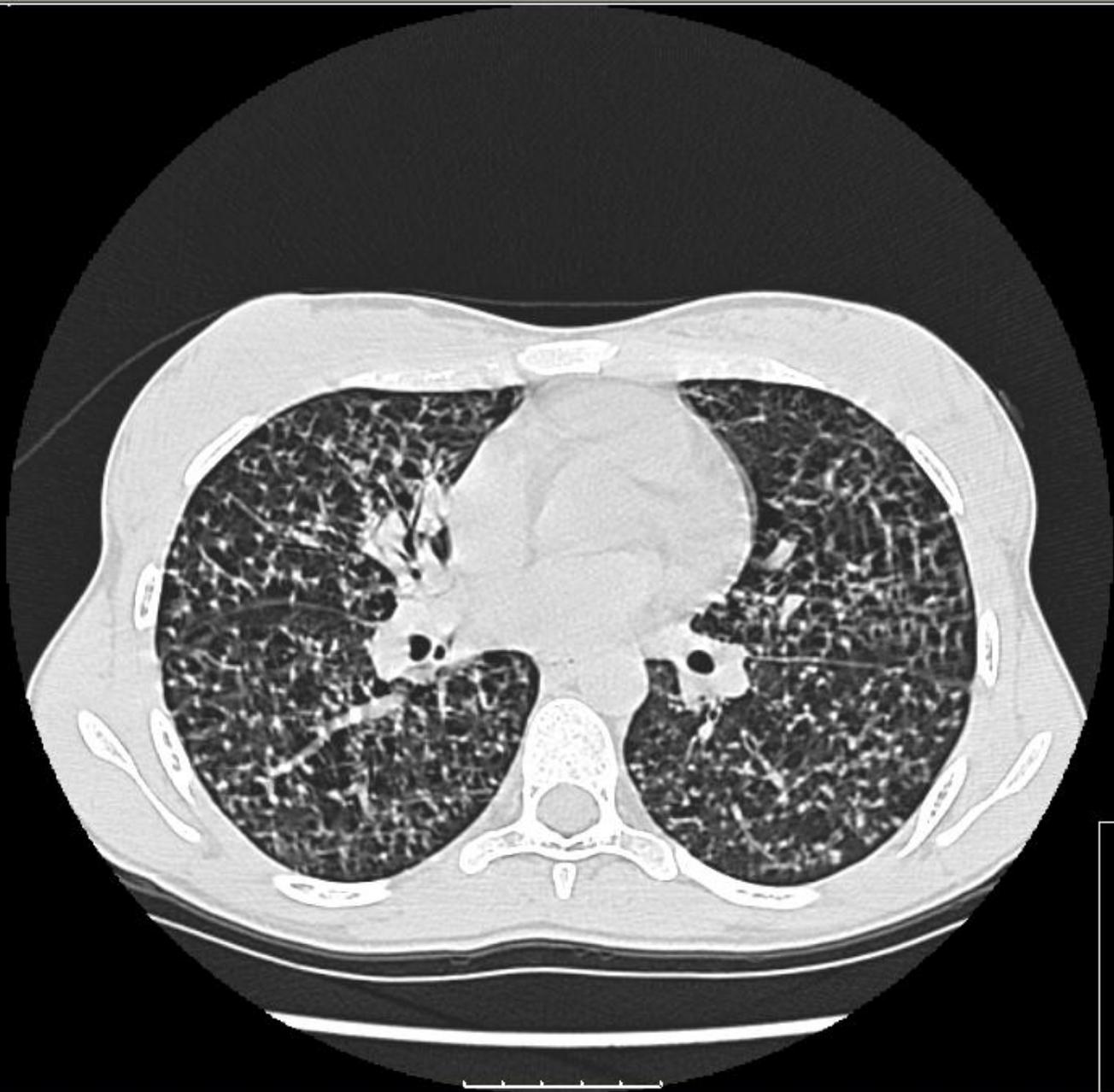






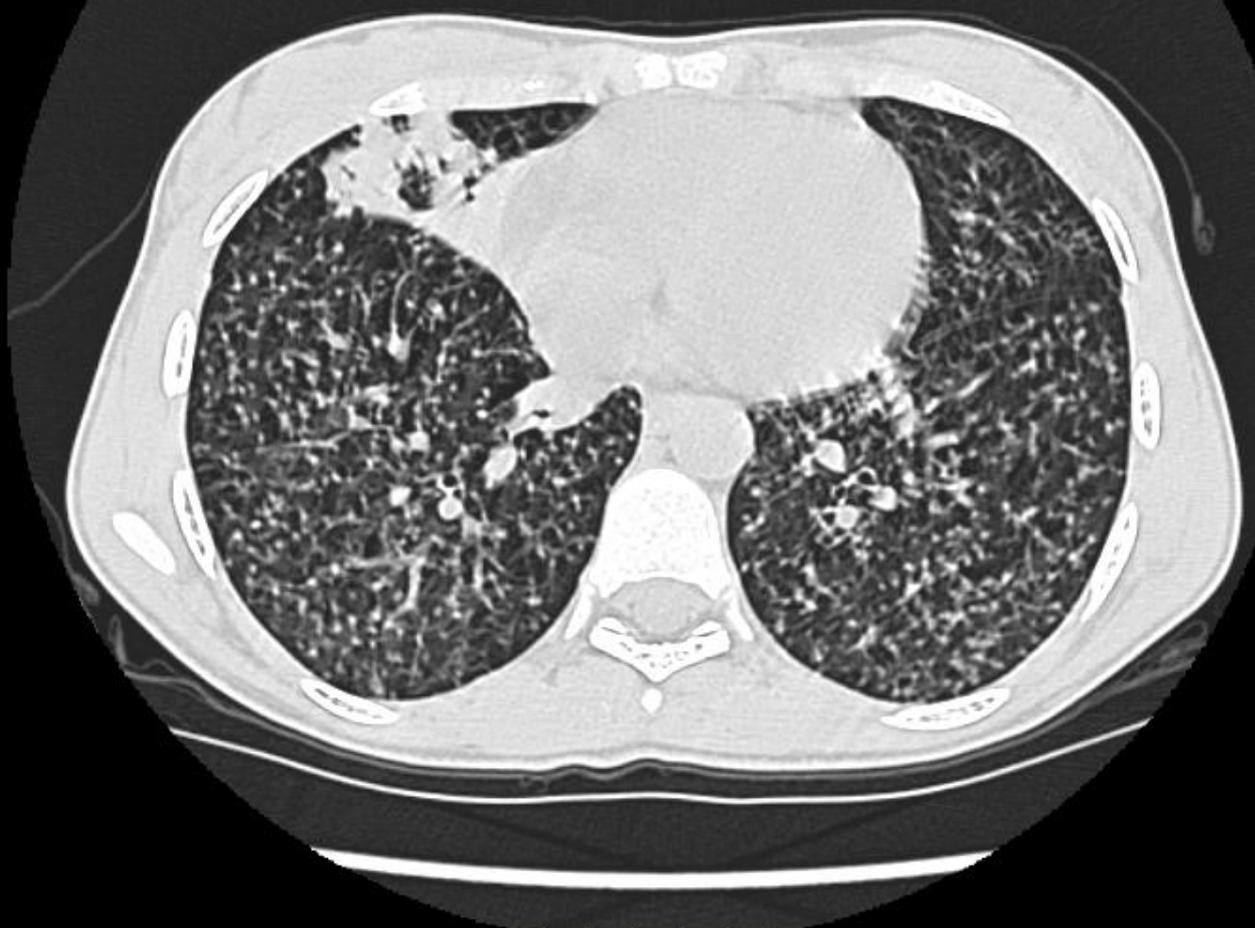


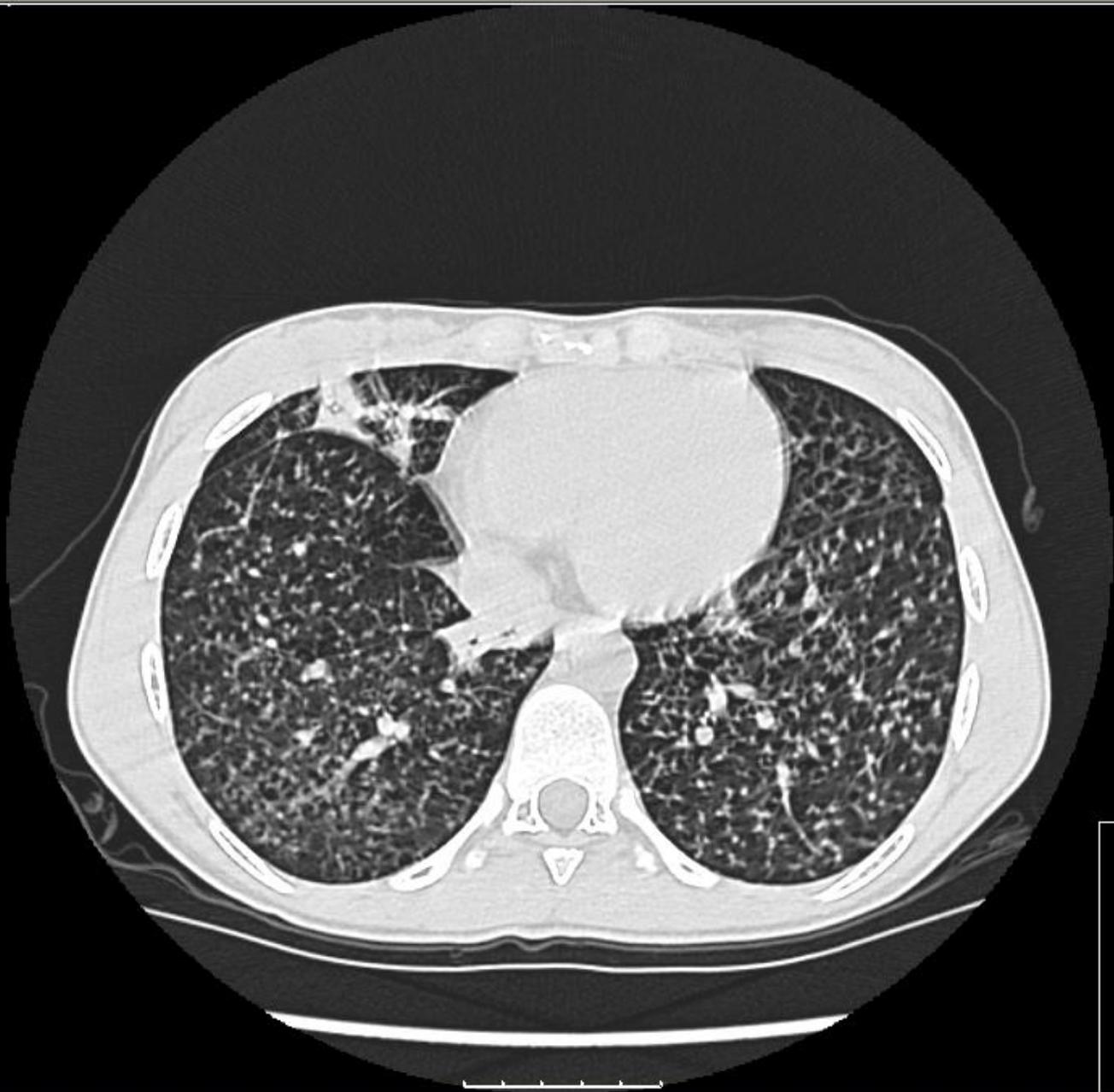


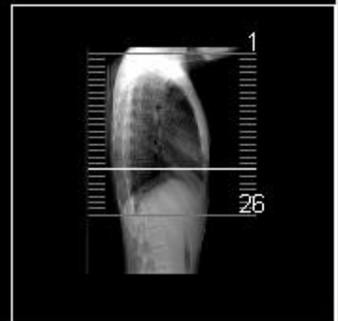
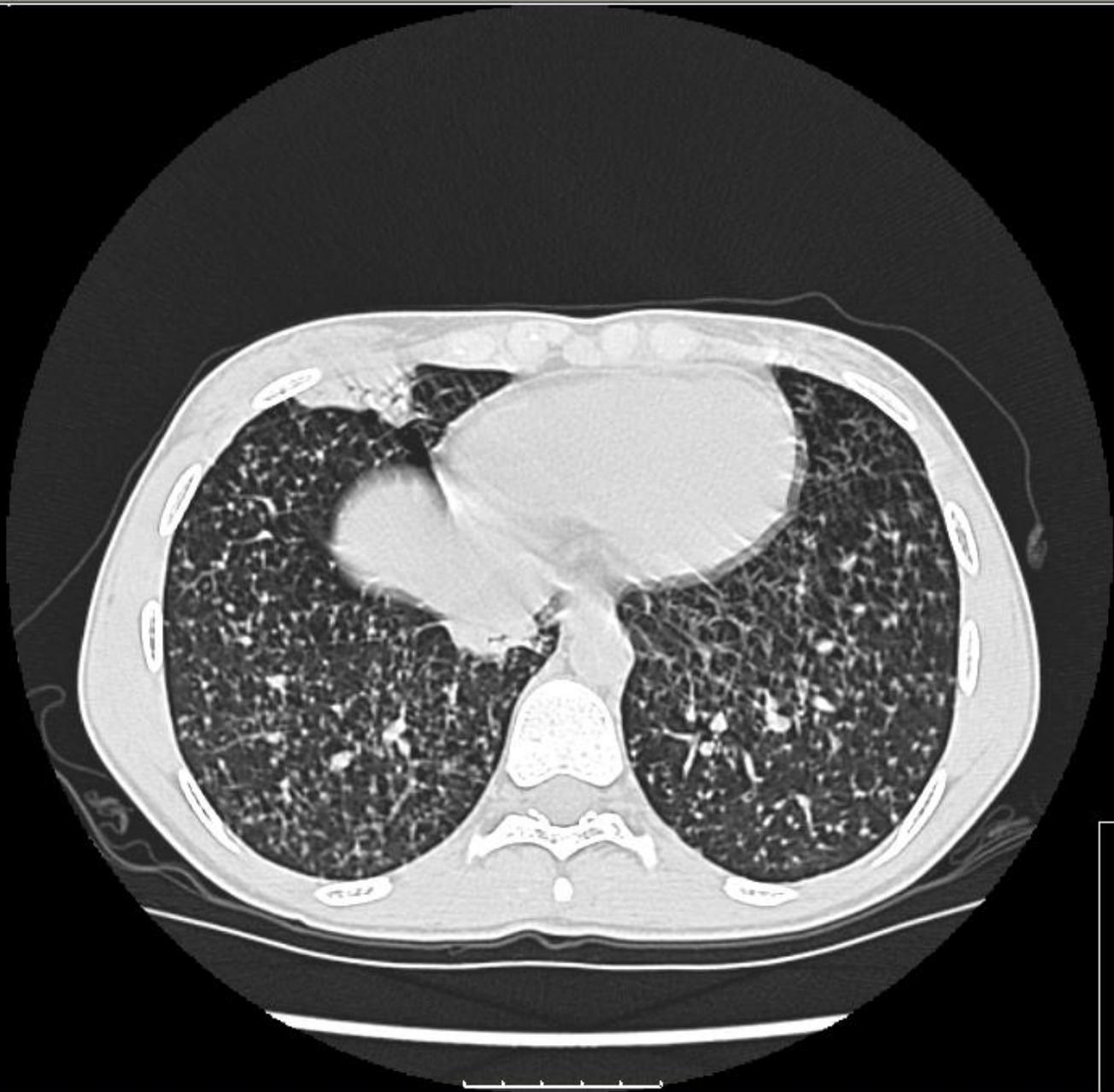


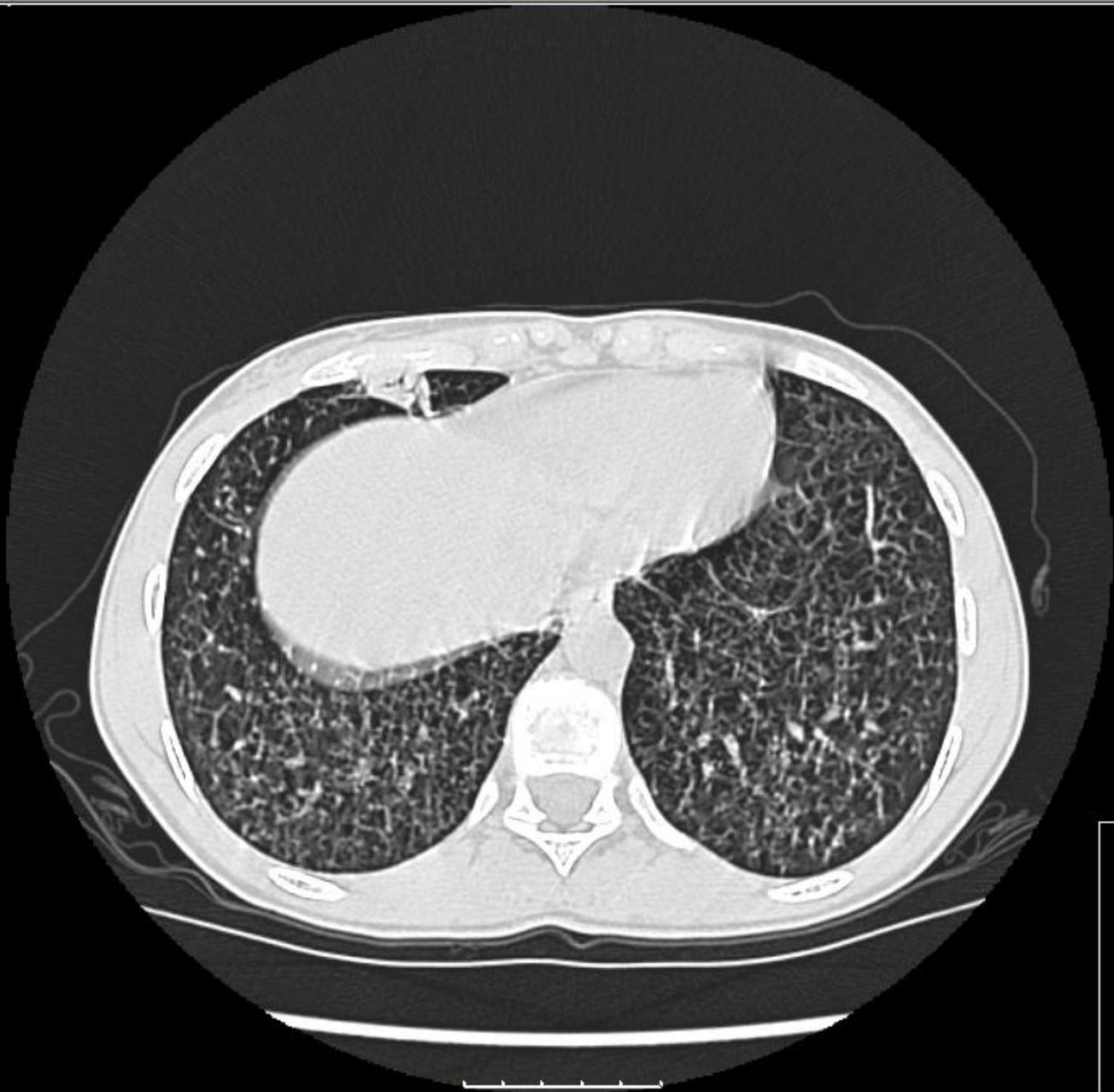


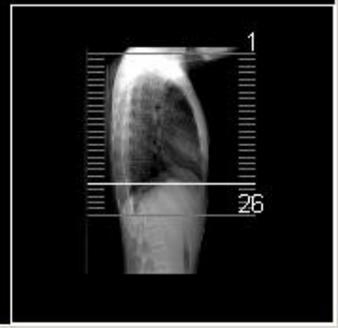
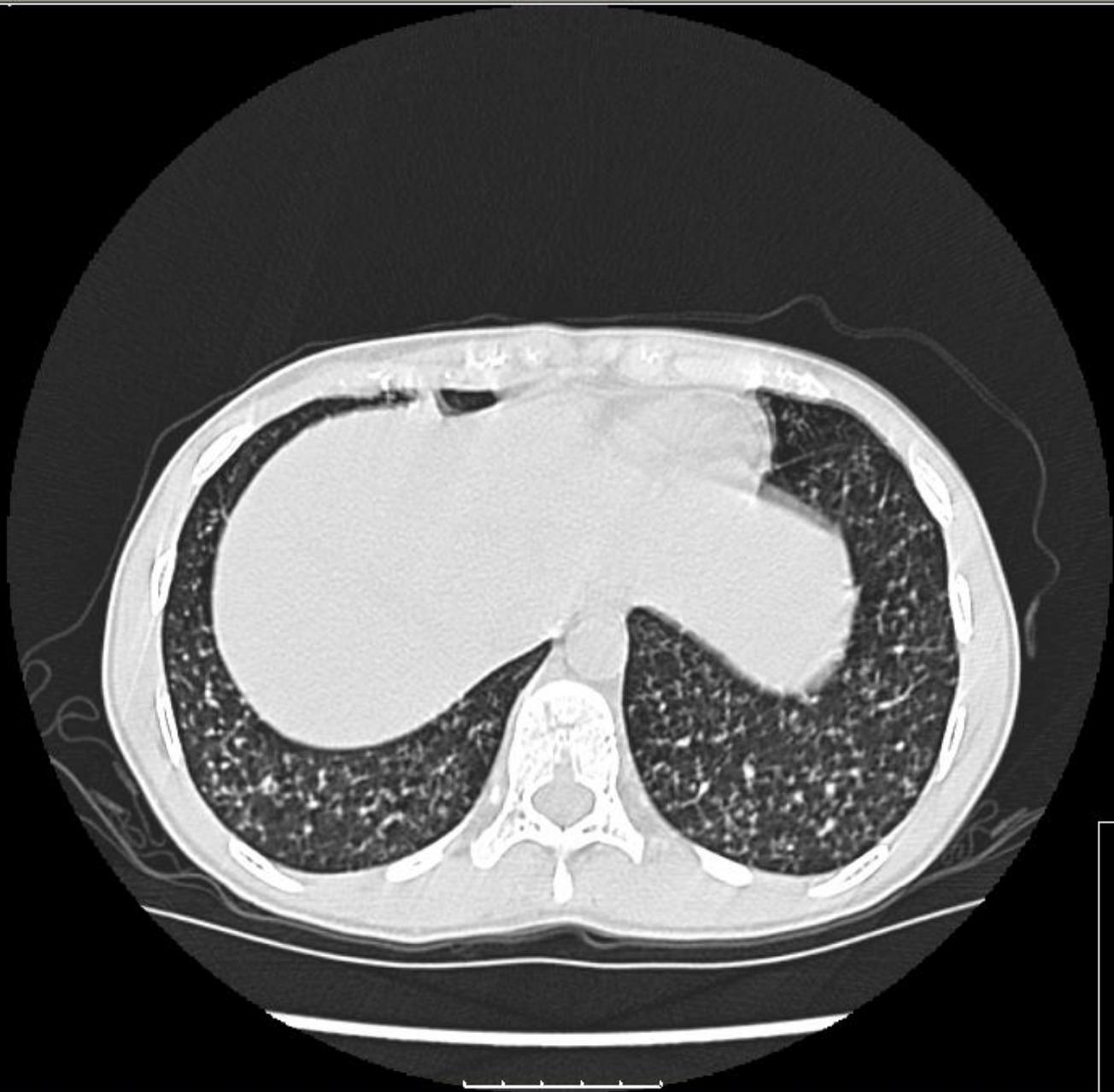


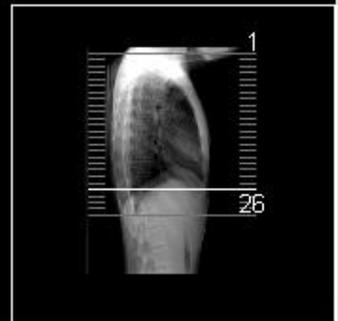
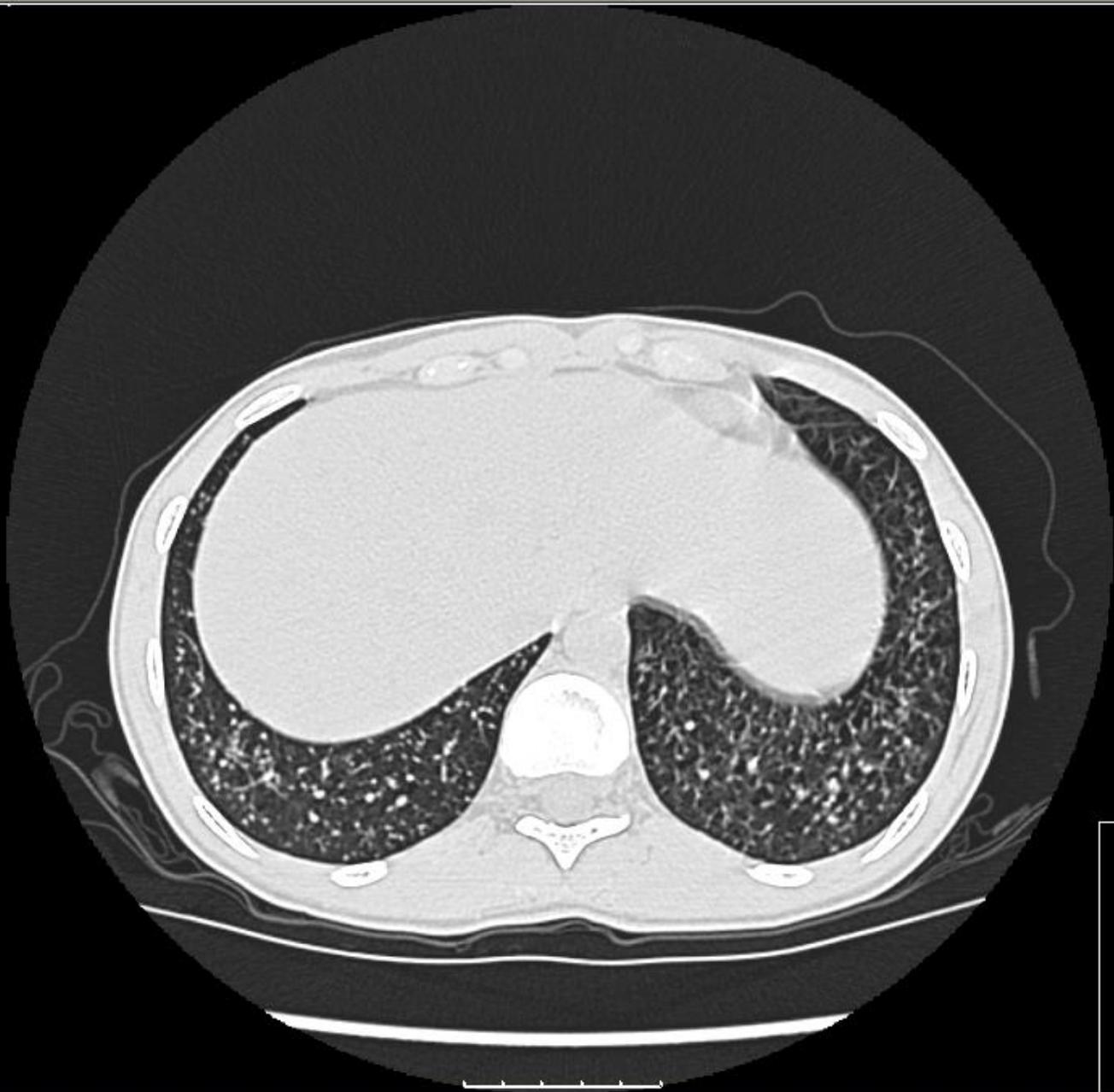


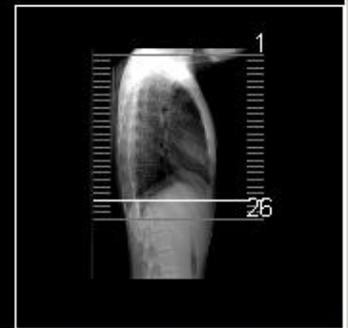
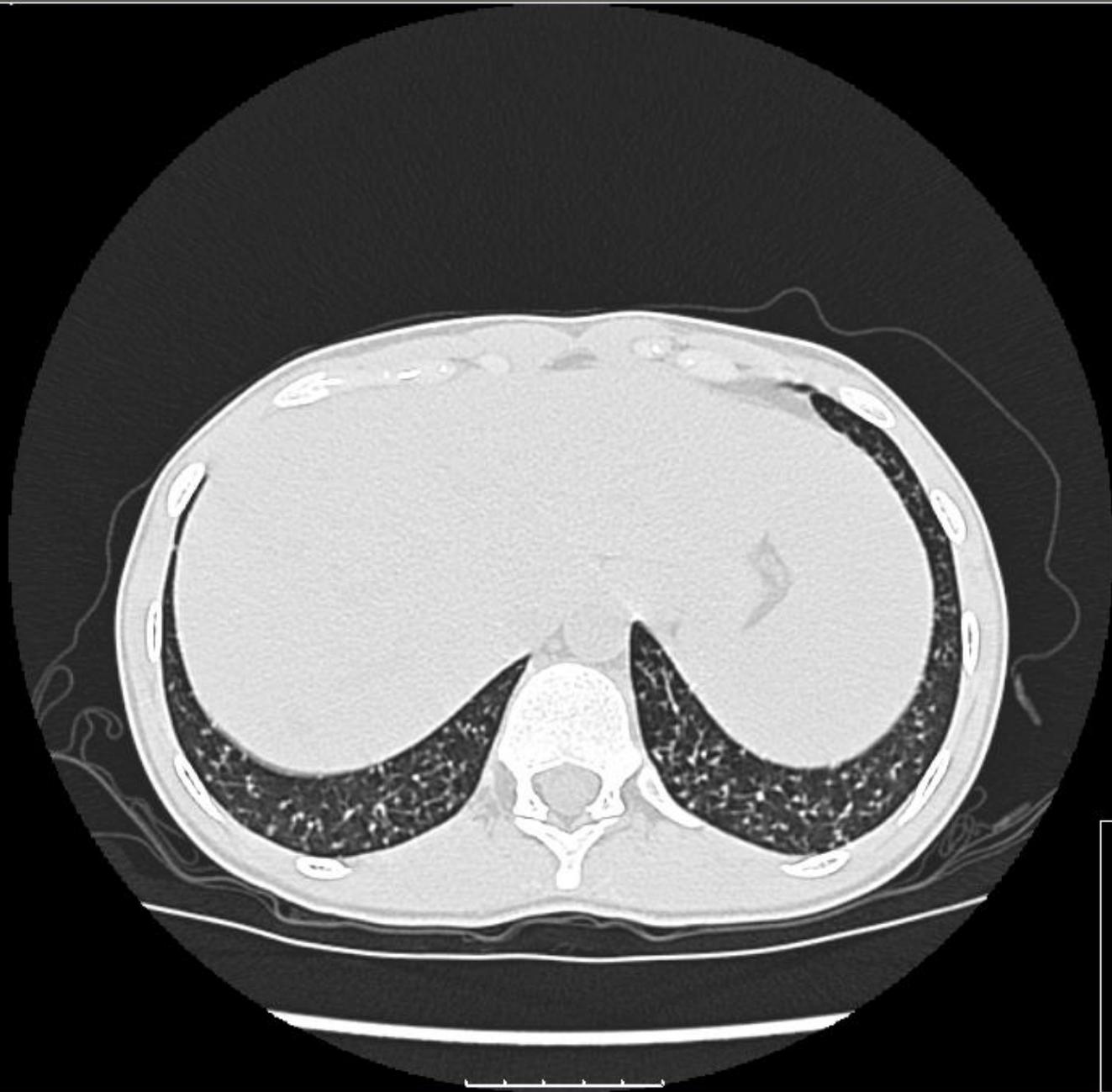


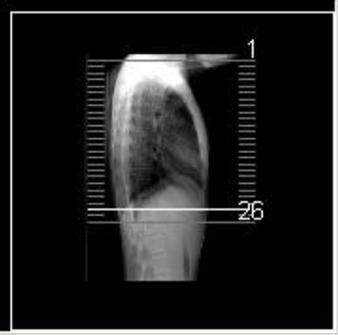
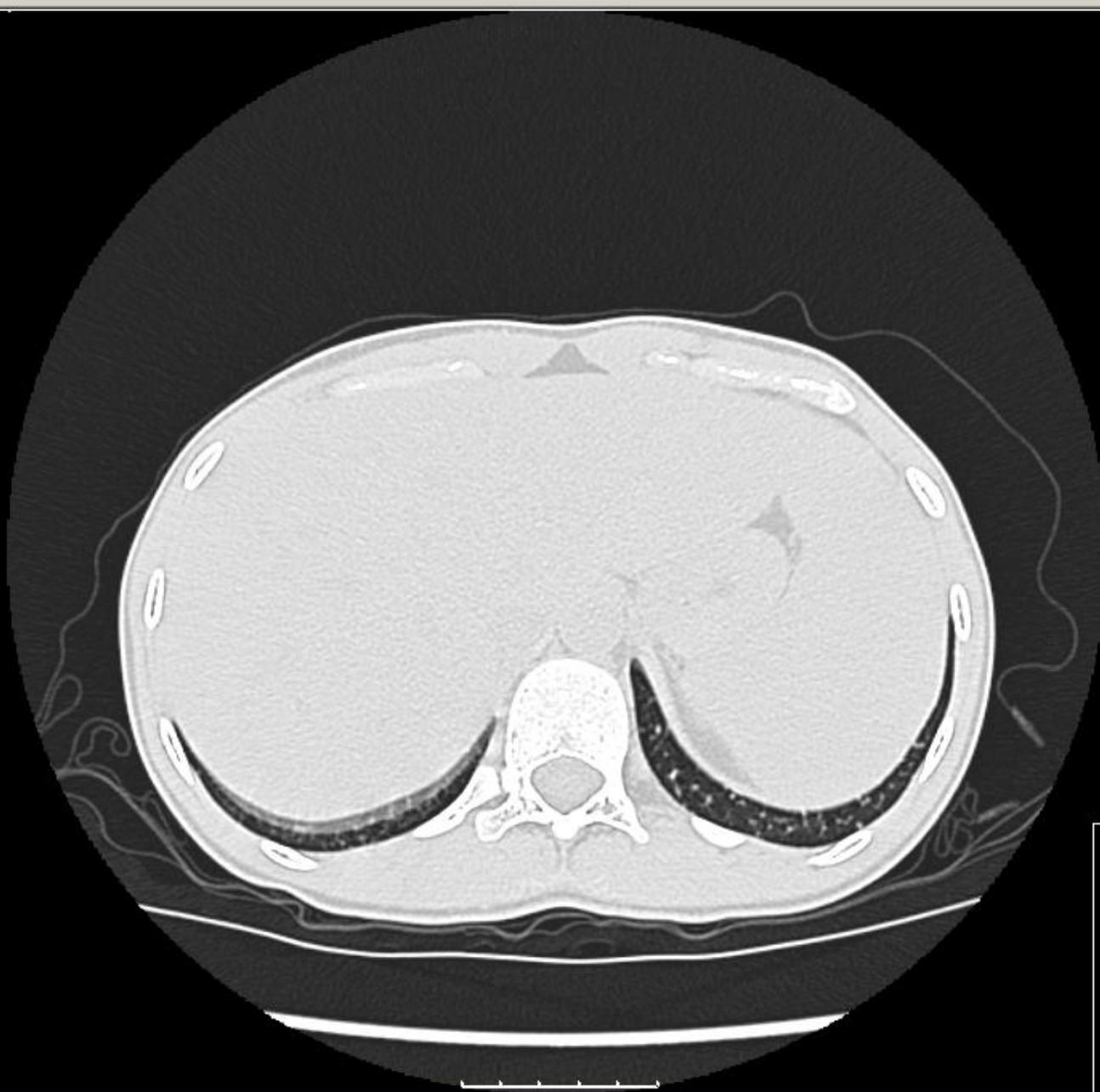


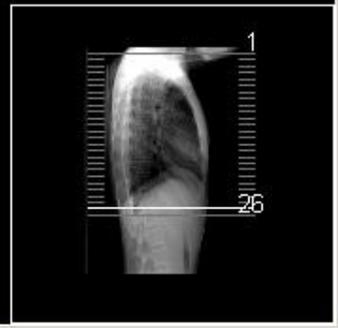
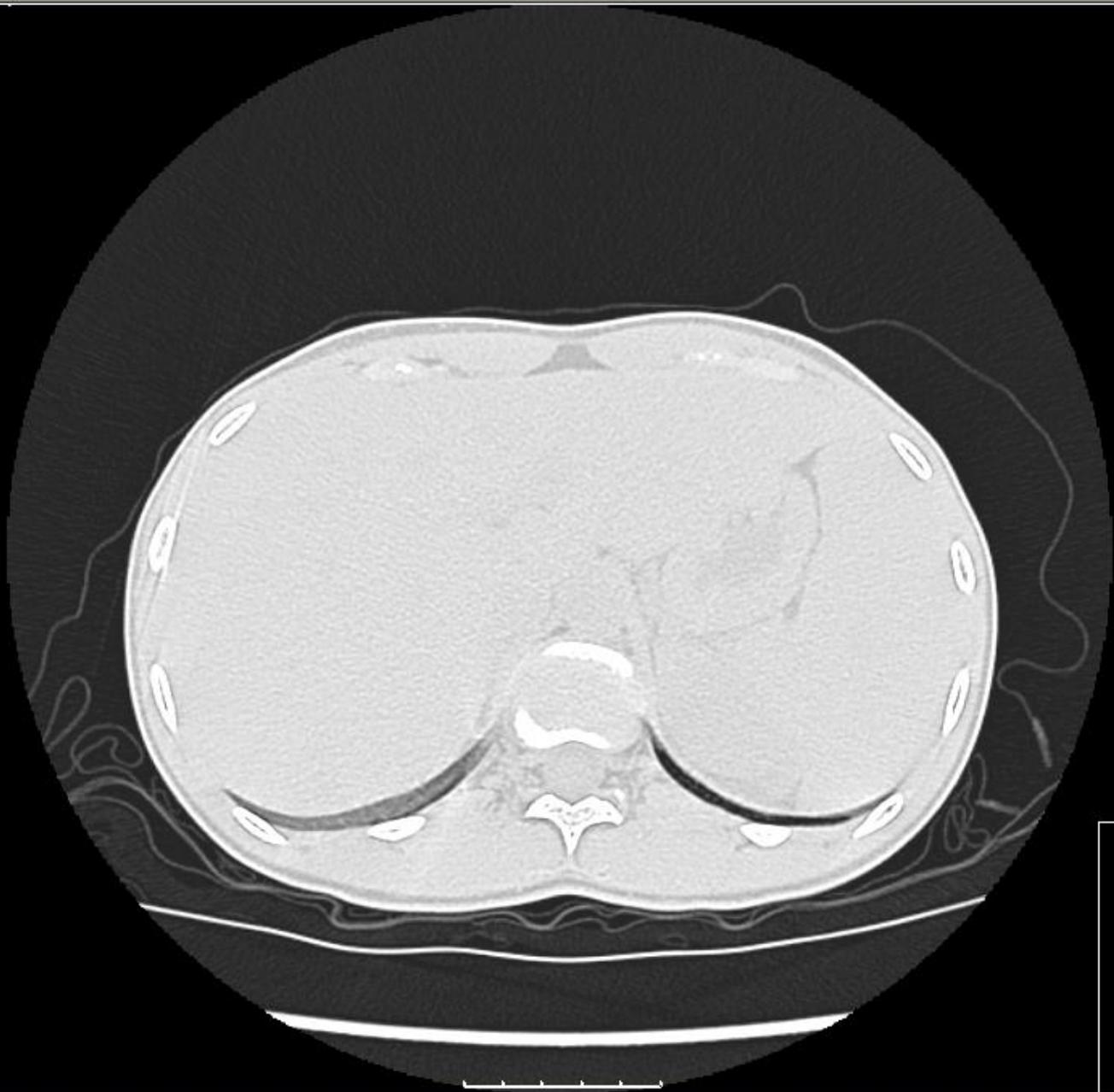








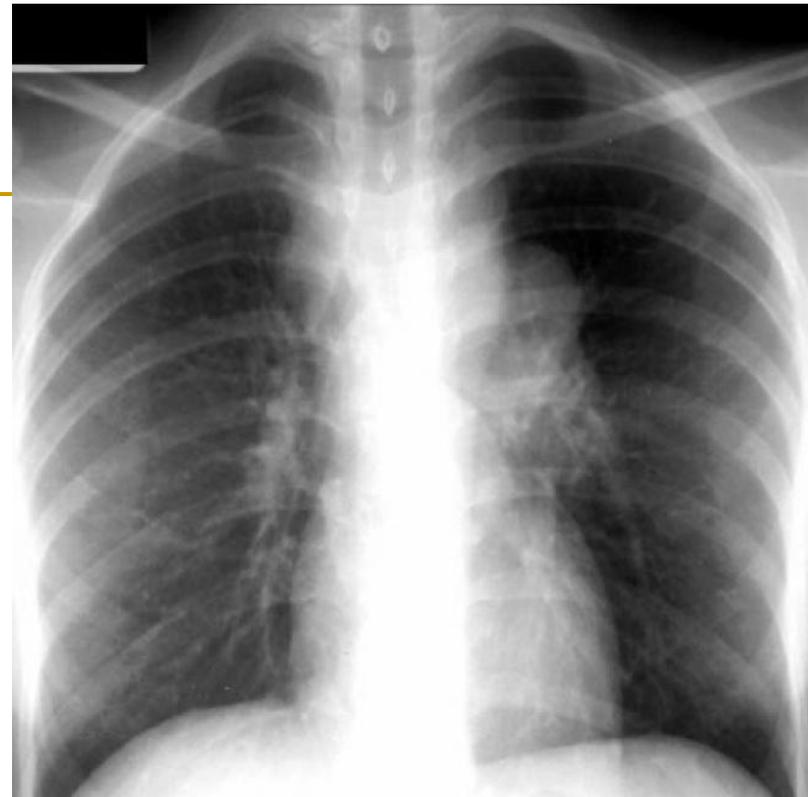




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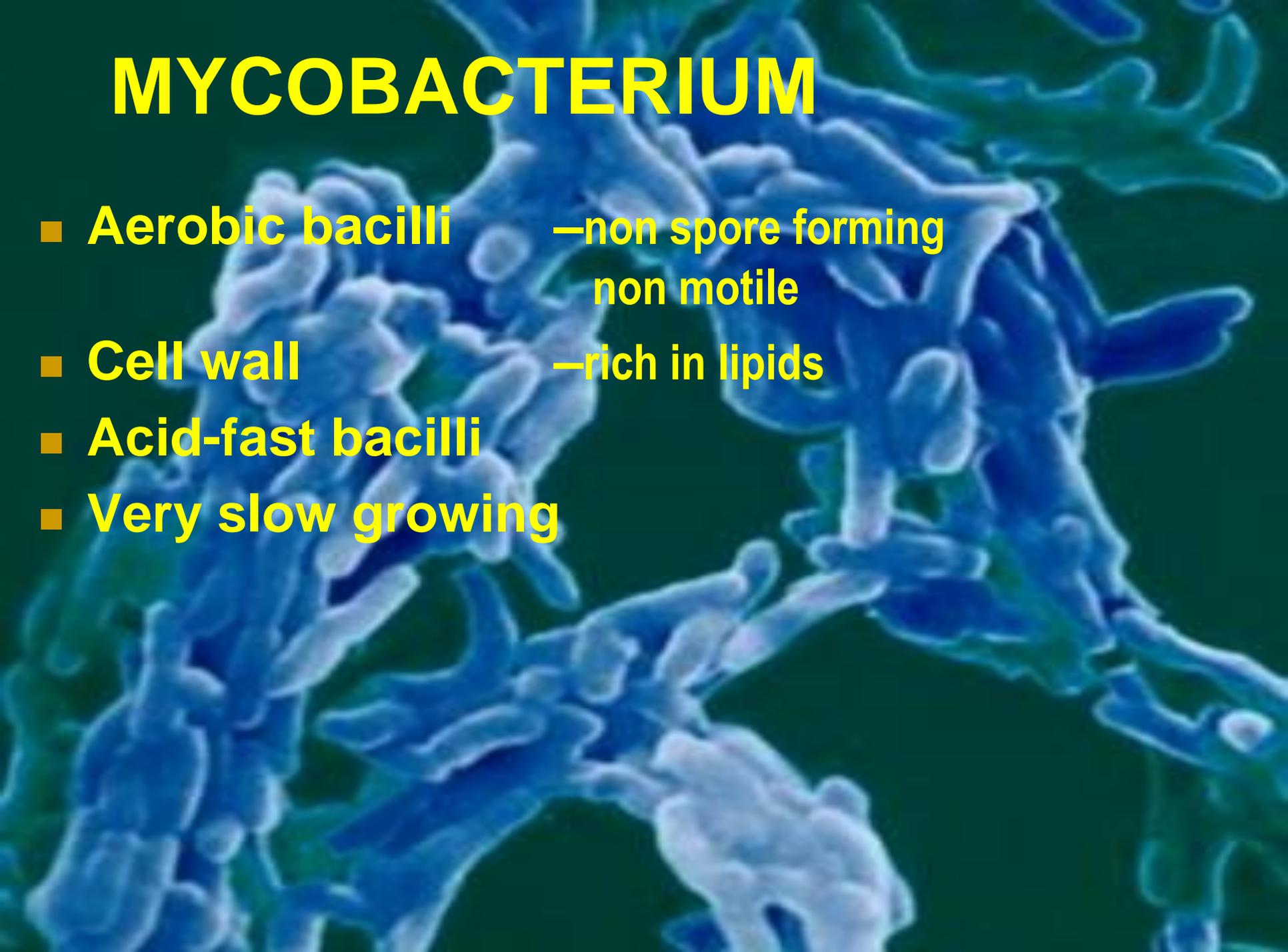
- 26.04.06. RD:
- Infiltratio pulmonis bilateralis in prim. in dex. / TB obs. pro.

Tuberculosis



What is Mycobacterium?

MYCOBACTERIUM



- **Aerobic bacilli** –non spore forming
non motile
- **Cell wall** –rich in lipids
- **Acid-fast bacilli**
- **Very slow growing**

TB: History

- Earliest Archeological Evidence of Spinal TB is from Egyptian Mummies, 4000 BCE.
- Earliest Evidence of Pulmonary TB 1000 BCE in a 5 Year old Boy
- Earliest Written Description 668-626 BCE: *The Patient Coughs Frequently, His sputum is Thick and Sometimes Contains Blood. His Breathing is Like a Flute, His Skin is Cold but His Feet are Hot. He Sweats Greatly and his Heart is Much Disturbed*

TB history

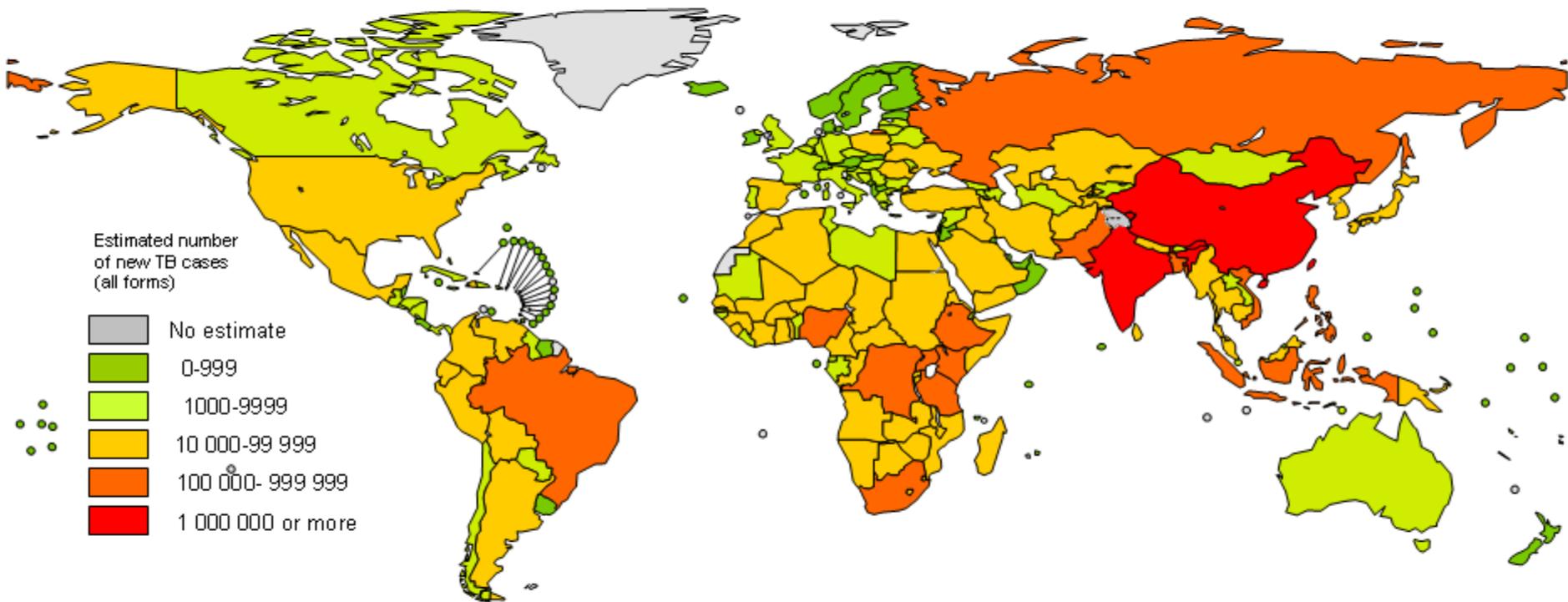
- TB Peak = Industrial Revolution 17th- 18th Century Resulting in 25-30% of all Adult Deaths in Europe
 - Until Robert Koch's discovery of the TB bacteria in 1882, many scientists believed that TB was hereditary and could not be prevented
 - Koch's discovery brought hopes for a cure but also bred fear of contagion
 - A person with TB was frequently labeled an outcast
-

Prevention is very important

- **Incidence declined before availability of anti-tuberculous drugs**
- **Improved social conditions - housing /nutrition**
- **Case detection & treatment**
- **Contact tracing**
- **Evidence of infection / disease**
- **Treatment of infected / diseased contacts**

ROLE OF IMMUNIZATION
BCG (bacillus Calmette Guerin)

Estimated numbers of new cases, 2005



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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Tuberculosis Epidemiology

~ 2 billion people are infected -

A Third of the World!

10% will develop active TB in their lifetime

→ 10 million new active TB / yr

→ 2 million deaths / yr



World Health
Organization

MYCOBACTERIA ASSOCIATED WITH HUMAN DISEASE

Mycobacterium	Environmental contaminant	Reservoir
<i>M tuberculosis</i>	No	Human
<i>M bovis</i>	No	Human, cattle
<i>M leprae</i>	No	Human
<i>M kansasii</i>	Rarely	Water, cattle
<i>M marinum</i>	Rarely	Fish, water
<i>M scrofulaceum</i>	Possibly	Soil, water
<i>M avium intracellulare</i>	Possibly	Soil, water, birds
<i>M ulcerans</i>	No	Unknown
<i>M fortuitum</i>	Yes	Soil, water, animals
<i>M chelonae</i>	Yes	Soil, water, animals

CLASSIFICATION OF MYCOBACTERIA ASSOCIATED WITH HUMAN DISEASE

Mycobacterium	Clinical significance	Pigmentation	Growth
<i>M Tuberculosis , M bovis</i> <i>M ulcerans</i>	Strict pathogens	No	No
<i>M leprae</i>	Strict pathogen	-	-
<i>M marinum , kansasii</i>	Usually pathogenic	Photochromogens	slow
<i>M scrofulaceum</i>	Rarely pathogenic	Scotochromogens	slow
<i>M avium intracellulare</i>	Pathogenic in immunocompromised	No	slow
<i>M fortuitum, M chelonae</i>	Rarely pathogenic	No	'rapid'

Pathogenesis

- Inhaled aerosols

Engulfed by alveolar macrophages

Bacilli replicate

Macrophages die

- Infected macrophages migrate



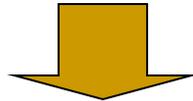
local lymph nodes

- Develop Ghon's focus



Primary complex

- Cell mediated immune response



stops cycle of destruction and spread

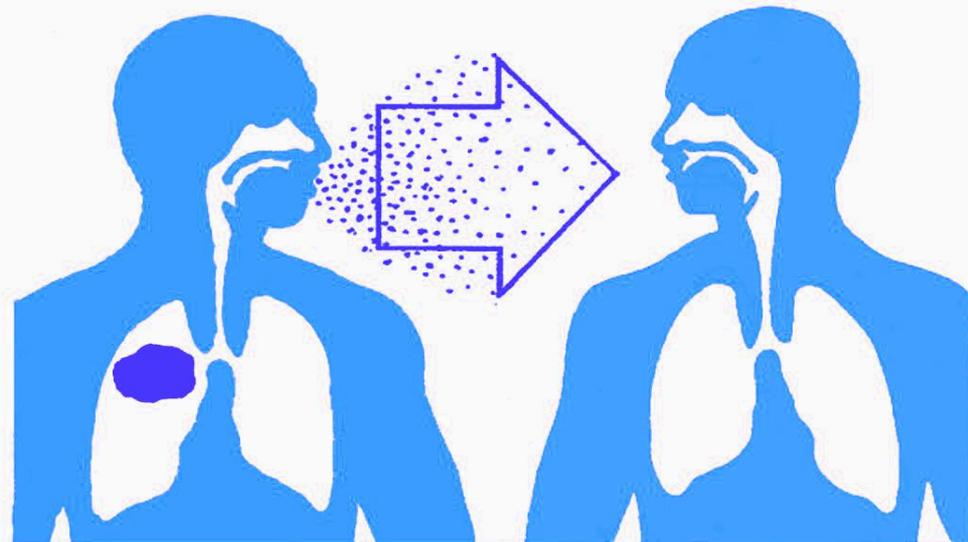
- Viable but non replicating bacilli present in macrophages

TB Infection vs. TB Disease

- There is a difference between TB “infection” and TB “disease”
- **TB infection:** TB germs stay in your lungs, but they do not multiply or make you sick
 - You cannot pass TB germs to others
- **TB disease:** TB germs stay in your lungs or move to other parts of your body, multiply, and may make others sick
 - can pass the TB germs to other people

Transmission & spread

- Spread by droplet nuclei
- Close contacts at highest risk of becoming infected
- Once infected, 5% will develop TB disease within a year or two and another 5% will develop disease later in life



How is it Spread?

- Is a person with microscopy positive TB in the sputum regarded as contagious?
 - YES
 - Should the above patient be hospitalized and isolated ?
 - Yes, as they are regarded as contagious they have to be hospitalized and isolated due to other weakened patients
 - When can the patients be discharged?
 - After 2 weeks relevant treatment
-

How is it Spread?

- Should a person positive culture and negative sputum microscopy for TB and no productive sputum be hospitalized ??
 - NO, only culture positive persons are not regarded as contagious.
 - Is ekstrapulmonal tuberkulose contagious?
 - It depends, generally not but wounds are highly contagiously !!!
-

So how Are TB Germs **NOT** Spread?

- Through quick, casual contact, like passing someone on the street
 - By sharing utensils or food
 - By sharing cigarettes or drinking containers
 - By exchanging saliva or other body fluids
 - By shaking hands
 - Using public telephones
-

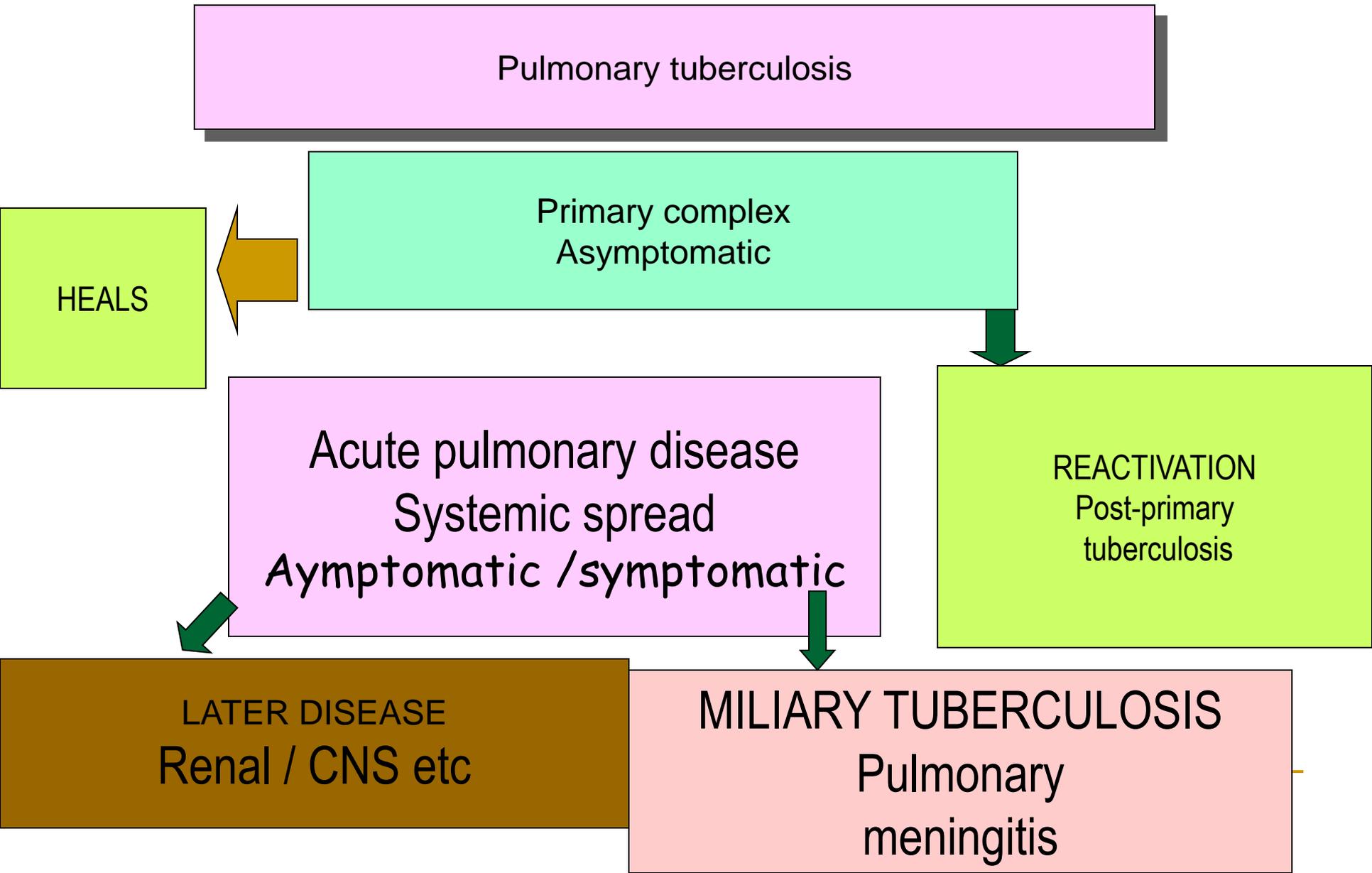
Medical conditions predisposing to active tuberculosis - once person infected with organism

- a) **HIV infection**
 - b) **Prior MTB (fibrotic changes on Chest X-ray)**
 - c) **Diabetes**
 - d) **Steroid or other immuno suppressive medications**
 - e) **Silicosis (remember job Hx)**
 - f) **Hematologic diseases, e.g. lymphoma**
 - g) **Dialysis patients**
 - h) **Post gastrectomy and malabsorption states**
-
- I) **Others, cancer etc.**

Common sites of TB disease

- Lungs
 - Pleura
 - Central nervous system
 - Lymphatic system
 - Genitourinary systems
 - Bones and joints
 - Disseminated (miliary TB)
-

Clinical presentation of TB



Pulmonary tuberculosis

Primary complex
Asymptomatic

HEALS

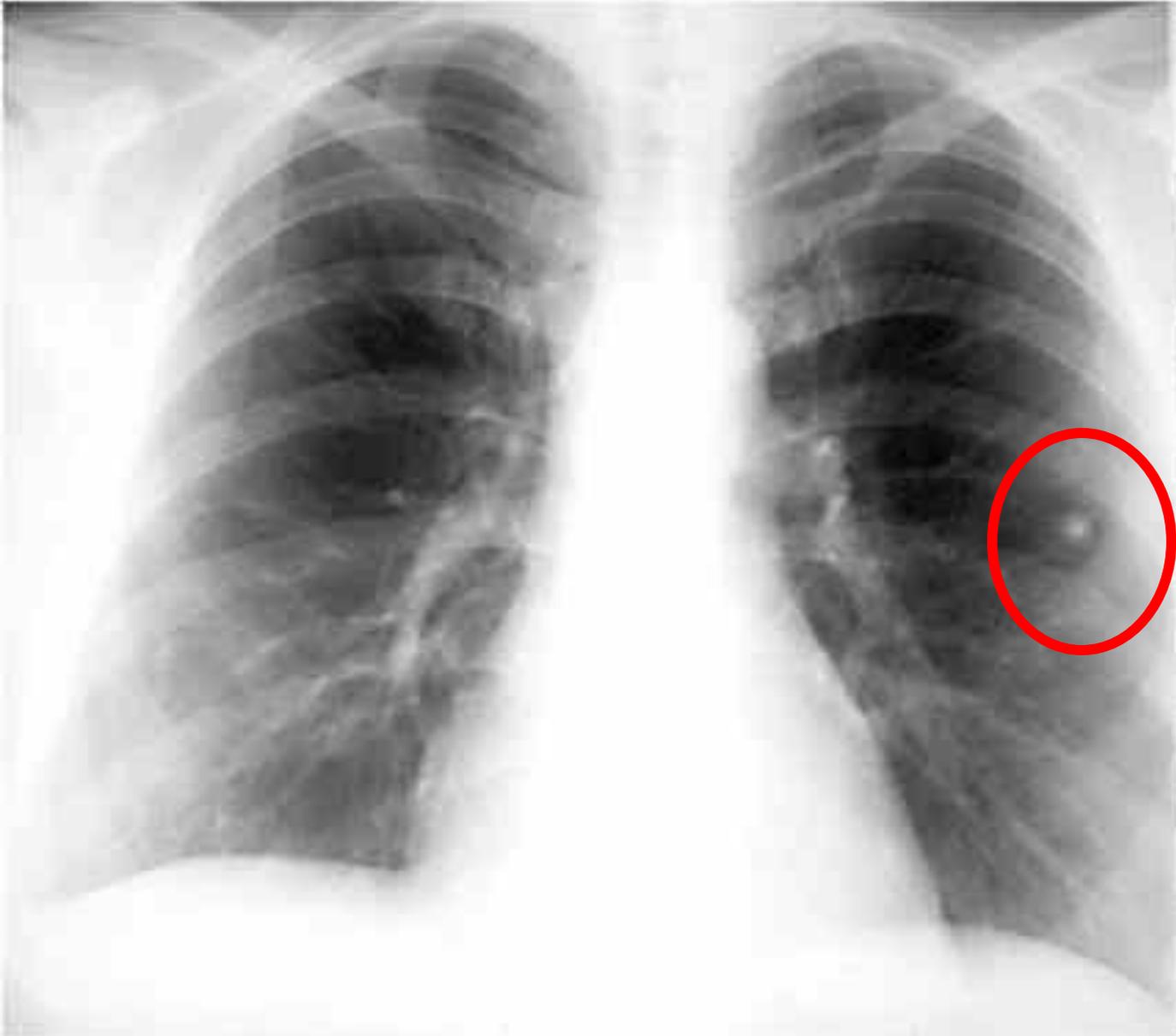
Acute pulmonary disease
Systemic spread
Aymptomatic /symptomatic

REACTIVATION
Post-primary
tuberculosis

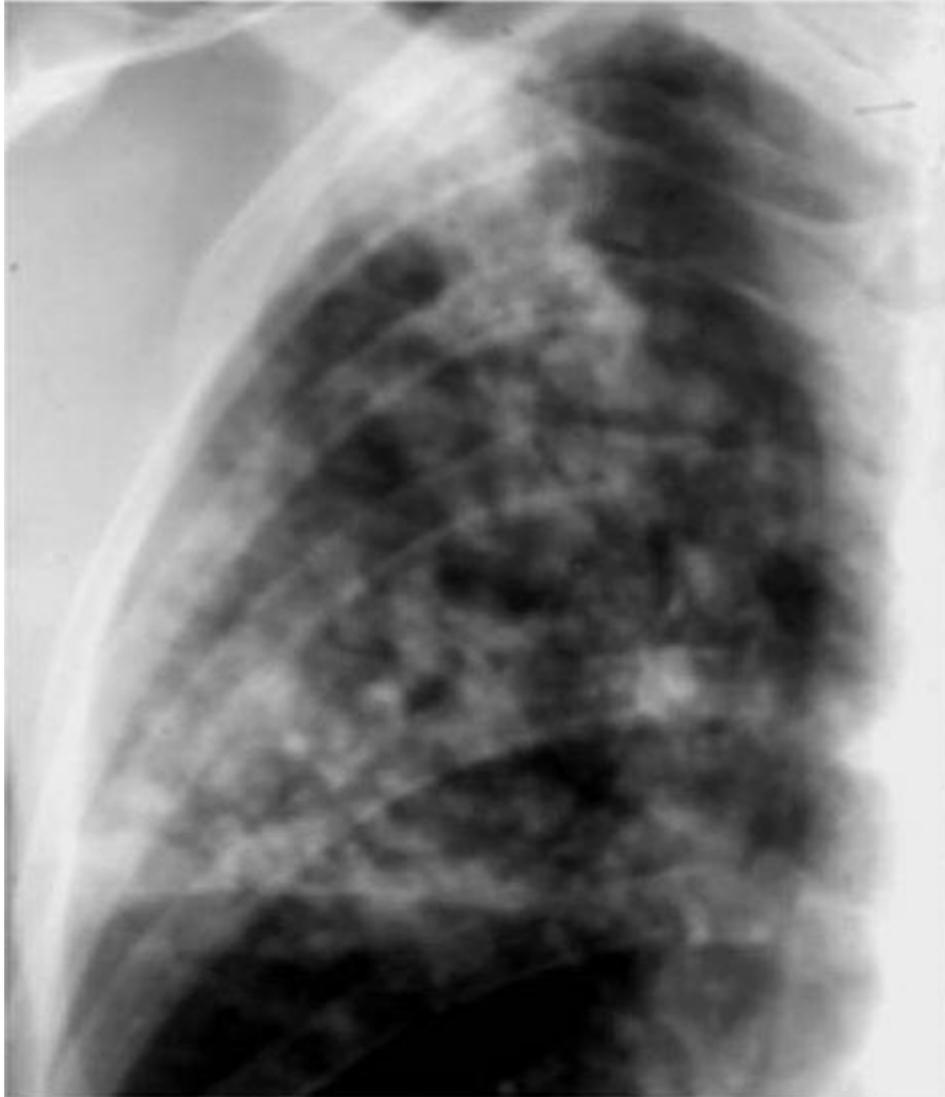
LATER DISEASE
Renal / CNS etc

MILIARY TUBERCULOSIS
Pulmonary
meningitis

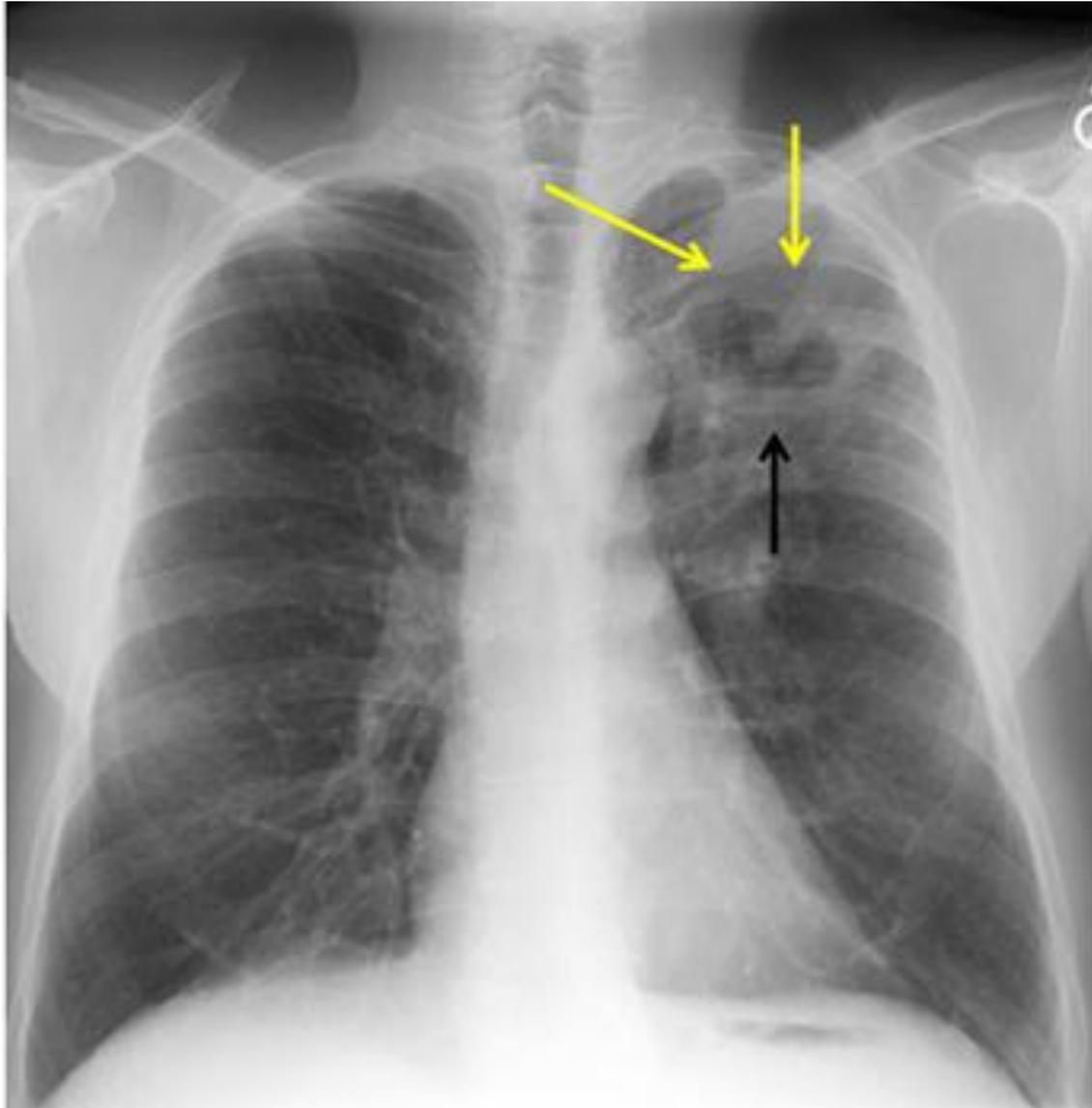
Ghon's focus



TB infiltrate



- Ill defined inflammatory exudation, circumscribed productive foci, and cavitation



- Consolidation
- Cavitation

Common Symptoms of TB Disease

Cough (2-3 weeks or more)

Coughing up blood

Chest pains

Fever

Night sweats

Feeling weak and tired

Losing weight without trying

Decreased or no appetite

If TB outside the lungs, pt may have other symptoms

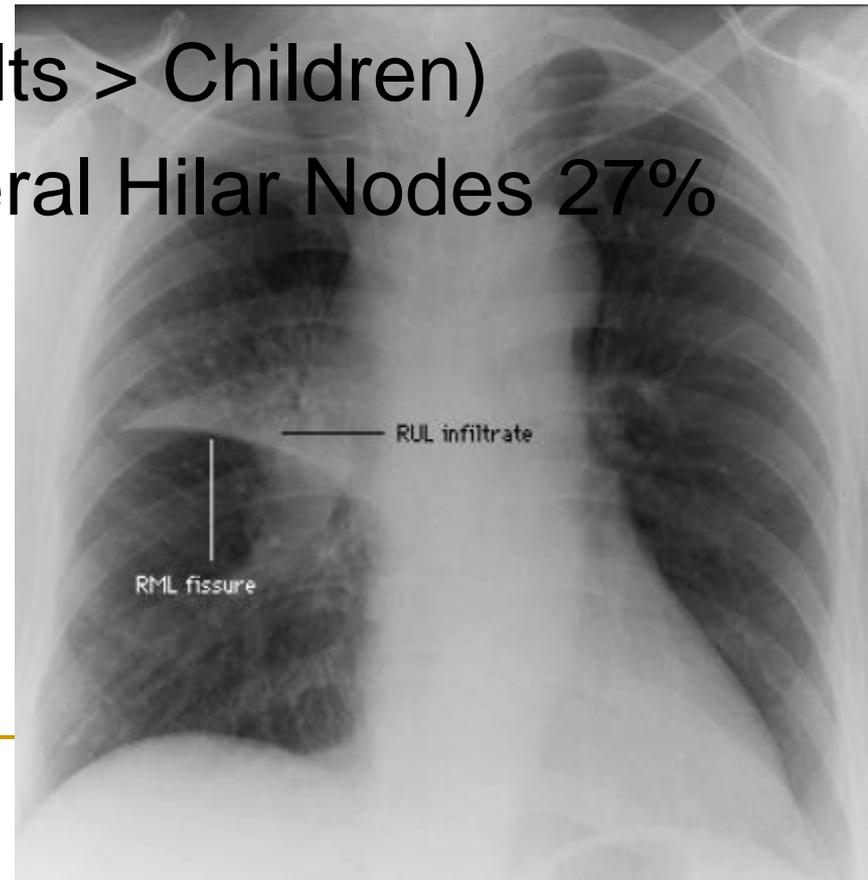
TB: Primary Chest X-Ray

Hilar Adenopathy 64% (Children > Adults)

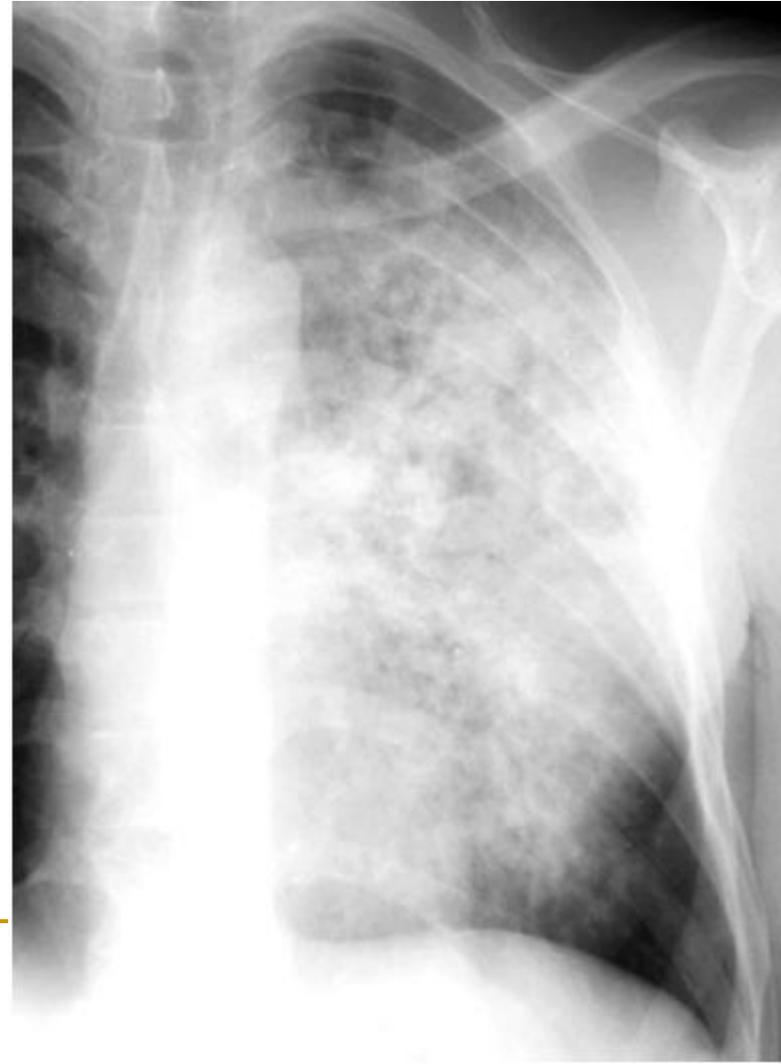
Hilar Changes Right > Left

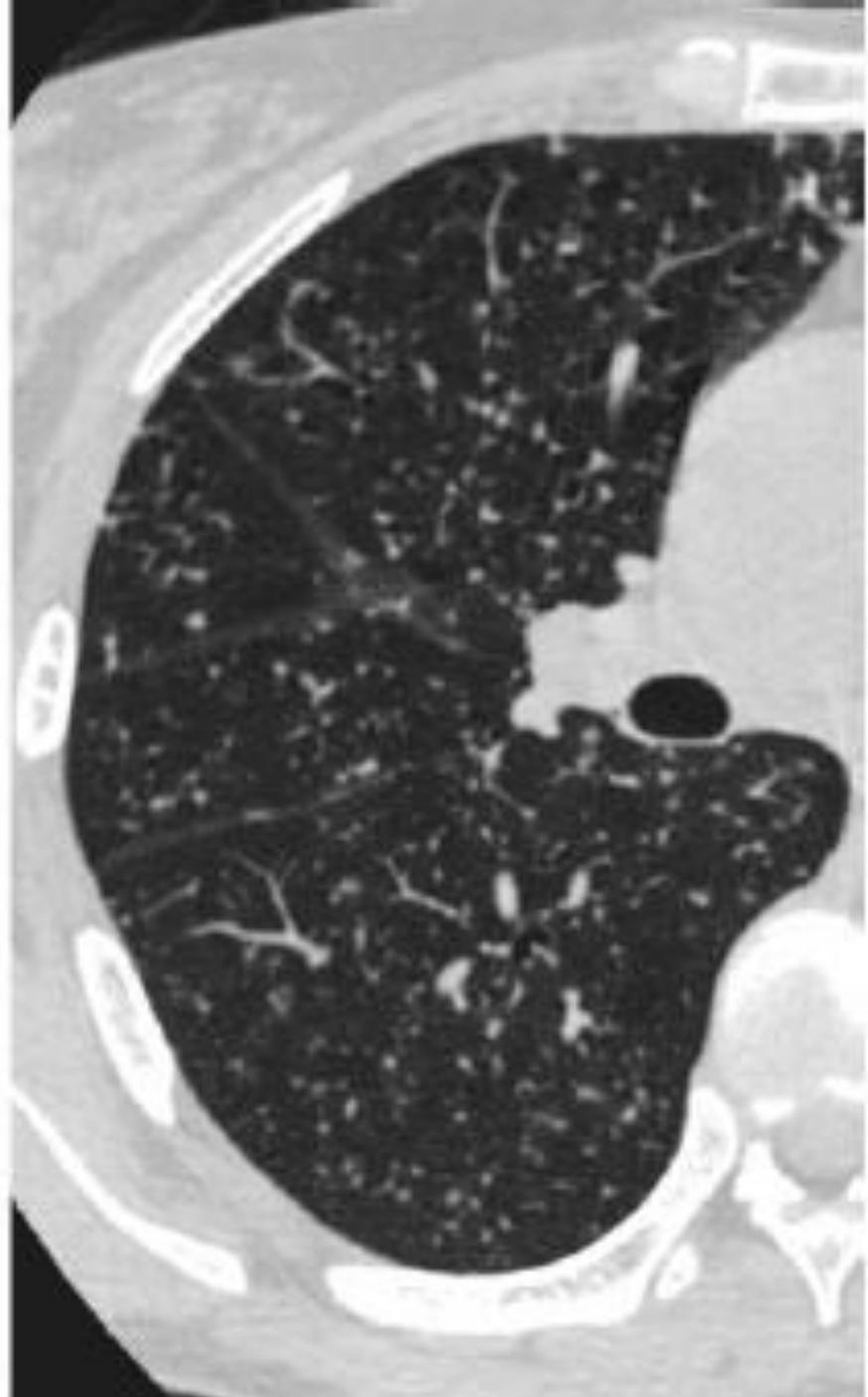
Pleural Effusion 29% (Adults > Children)

Unilateral Infiltrate/Ipsilateral Hilar Nodes 27%



- Parenchymal disease manifests as dense, homogeneous parenchymal consolidation in any lobe.

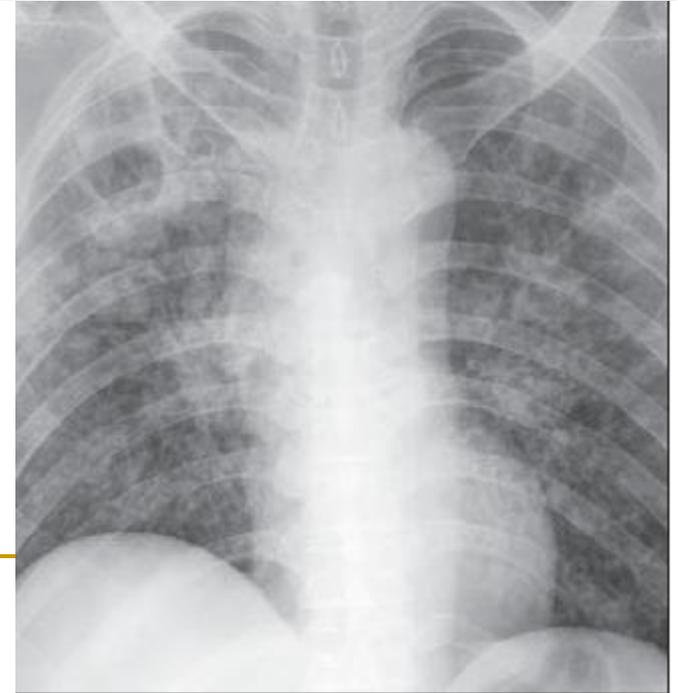




Miliary tuberculosis

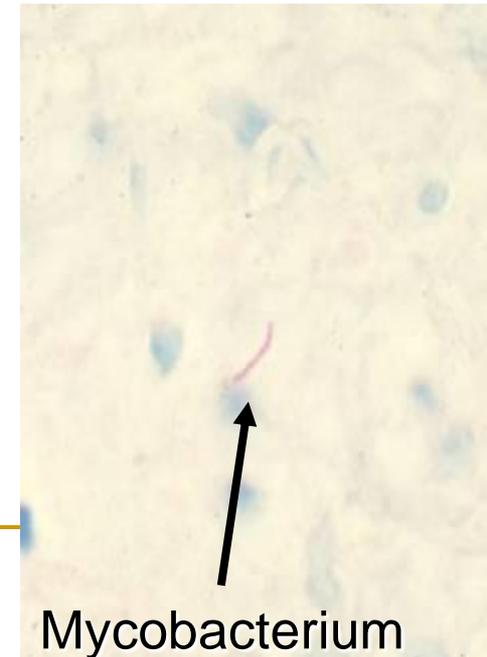
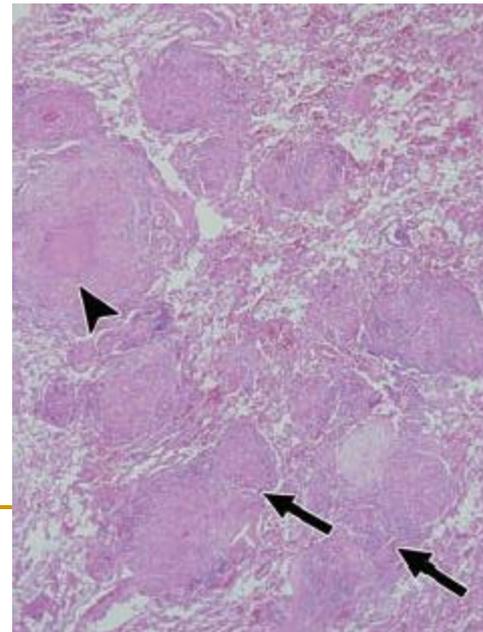
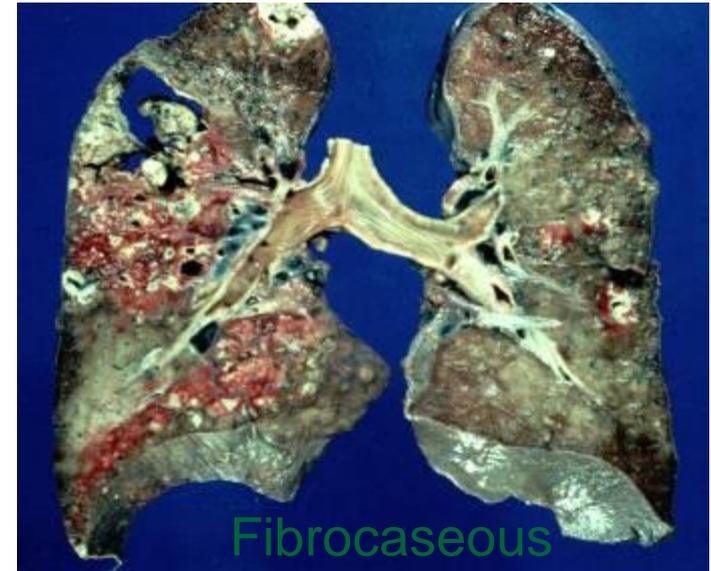
Summary

- Caused by *Mycobacterium tuberculosis*.
- Transmitted through inhalation of infected droplets
- Primary
 - Single granuloma within parenchyma and hilar lymph nodes (Ghon complex).
 - Infection does not progress (most common).
 - Progressive primary pneumonia
 - Miliary dissemination (blood stream).



Summary

- Secondary
 - Infection (mostly through reactivation) in a previously sensitized individual.
 - Pathology
 - Cavitory fibrocaceous lesions
 - Bronchopneumonia
 - Miliary TB



Summary continue

Primary Tuberculosis

- ** First exposure to MTB often asymptomatic
- ** Typically pul. Infiltrates: all lung fields with or without hilar adenopathy, these infiltrates non-specific in appearance and not cavitary
- ** In most cases pneumonitis clears without specific therapy and latent infections established
- ** In some cases, primary infection may progress, resembling reactivation disease

Latent Infection

- ** following primary infection many persons remain asymp.
- ** Organisms remain latent within macrophages indefinitely
- ** Tuberculosis skin test (T-PPD) - very important to discover these persons
- ** If no preventive therapy given, 1:10 persons with MTB infection will develop clinical disease at some time in their lives

Reactivation Tuberculosis

- ** Constitutional sx and generalized wasting
 - ** Weight loss
 - ** Fever at night, sweating
 - ** Diagnosis maybe difficult as pul sx mild or lacking.
-

But when to treat TB!?

“Diagnosis, diagnosis & diagnosis” William Osler

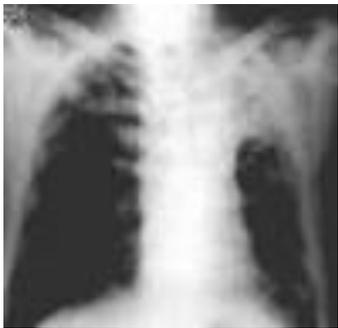
Objectives for TB treatment and control

Based on clinical suspicion but always verify the diagnosis !!!!!!!!!!!!!!!!!!!!!!!

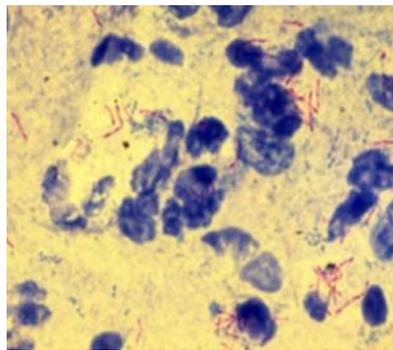
Microbiology

maybe histology

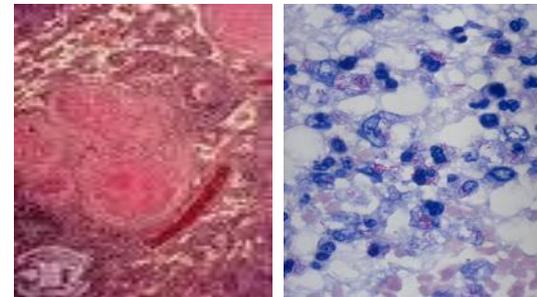
- To rapidly diagnose patients with active TB and treat them correctly to eliminate danger of spread.
- To have rapid diagnostic methods, with high sensitivity and specificity to diagnose diseased patients at the beginning of the symptoms for an adequate treatment prescription



Clinical suspicion



Microbiology



Histology

**“Diagnosis, diagnosis & diagnosis”
William Osler**

High index of suspicion is essential

MTB manifestations are unspecific thus lab. confirmation is essential

Close communication between the clinician and microbiology lab. is mandatory to identify microorganism causing disease and determine their susceptibility to antimicrobial agent that assist in their eradication.

Tuberculosis skin (PPD, mantoux) test important first step in identifying infected Patients

Lab. Techniques for MTB identification:

- * A.F.B. smear and cultures of resp. secretion (e.g. sputum)**
- * A.F.B. smear and cultures of potentially infected body fluids or tissues:
CSF, gastric fluid, urine, LN BX bone marrow BX, joint fluids, etc.**
- * ~~Rapid methods: PCR (polymerase chain reactions) and nucleic acid probes~~**

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Microbiology

MTB: fastidious, slowly growing, **acid alcohol fast**, aerobic bacterium (AFB) (56 days before its for sure negative)

Cell wall composed of complex peptidoglycans and long chain lipids

These lipids make MTB hydrophobic thus resistant to many stains routinely used in Laboratory, e.g. Gram & Giemsa stains as well as AA fastness

(Once stained, cannot be decolorised by alcohol, acid solutions)

AFB smear



AFB (shown in red) are tubercle bacilli

False negative results

- **Inadequate sputum collection**
 - avoid – saliva, nasal discharge**
 - collect – bronchial sputum from depth of chest**
- **Inadequate storage of sputum / stained smears**
 - exposure to direct sunlight**
 - radiation (UV light)**
 - excessive heat / humidity**
- **Not taking mucopurulent portion of sputum**
- **Inadequate smear preparation**
- **Inadequate smear examination**
- **Administrative & recording errors**

False positive results

- **Food particles**
- **Precipitated stains**
- **Saprophytic AFB**
- **Spores of *B.subtlis***
- **Fibres and pollen**
- **Scratches on slide**
- **Contamination through carry over of AFB from one smear to another**

Aims of sputum culture

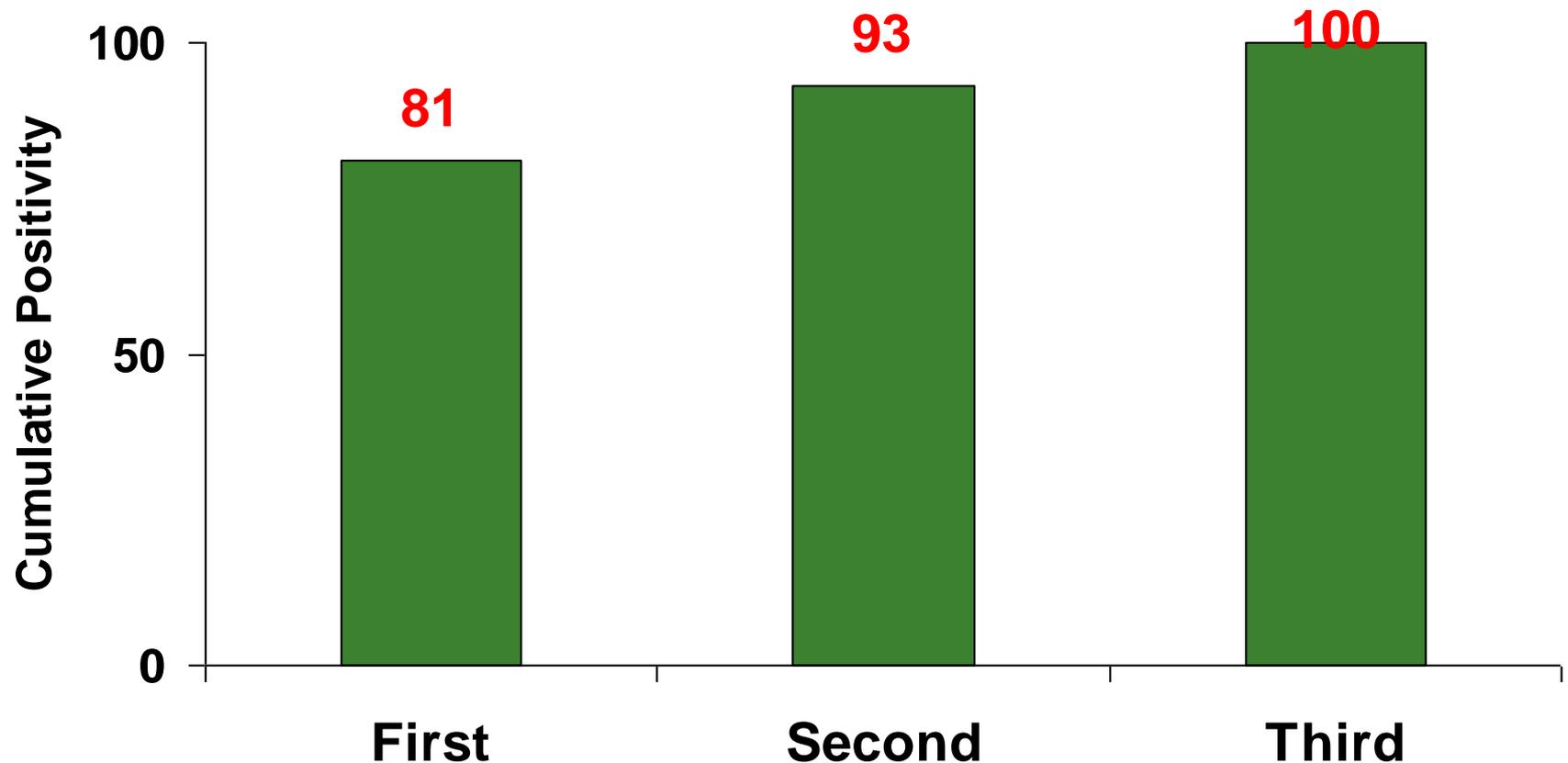
Diagnosis of patients with infectious tuberculosis

Monitoring progress of patients on treatment

Questions

- How many sputum cultures for TB is necessary?
- 1
- 2
- 3
- 4
- 5

Three cultures and smears are optimal



TB: Tests and Diagnosis

PPD test/TST test*

*PPD = Purified Protein Derivative;

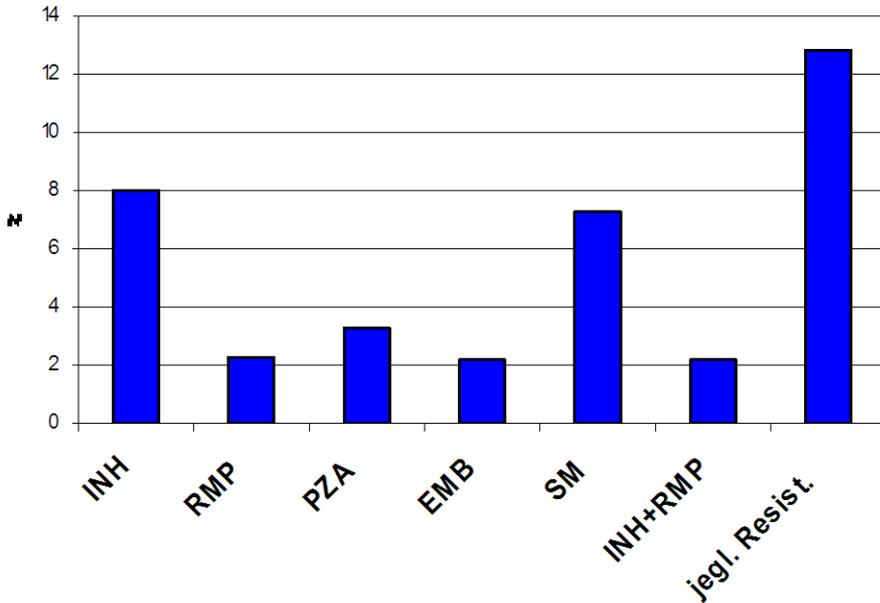
The Tuberculin Skin Test Identifies
Individuals who have been Infected with
Mycobacterium Tuberculosis, it does not
differentiate between Old and New
Infection

Treatment of Active TB Disease



Drug Susceptibility Testing

TB antibiotic resistance in Germany 2006



For all TB strains isolated, resistance has to be performed

DRUG THERAPY

First Line drugs:

- ** isoniazid (INH)
- ** Rifampicin (RIF)
- ** pyrazinamide (PZA)
- ** Streptomycin,
- ** ethambutol

Second line drugs: *

- ** capreomycin, ciprofloxacin
- ** cycloserine, ethionamide
- ** Kanamycin, ofloxacin
- ** Para-amino salicylic acid (PAS)

* *These drugs:*

- *less effective*
- *more expensive*
- *more toxic*

Drug therapy

Commonly Used Regimens to treat TB

- a) Initial phase (first two months) 3-4 drugs
INH, RIF, PZA, Streptomycin or Ethambutol
- b) Continuation phase (3-10 months)
INH, RIF

Duration of Drugs Therapy for TB

Depends on the site of disease;

** Pulmonary TB - 6 months

** Extra pulmonary TB

TB Meningitis

Bone / Joint

Disseminated Disease

} 2 months with 4 drugs + 10 months with INH +RIF

Toxicities of TB Treatment

Important

All therapies have significant toxicity

All drugs are associated with hepatitis and hypersensitivity reactions

Unique toxicities

- INH: hepatic necrosis, peripheral neuropathy
- Rifampin: altered drug metabolism
- Pyrazinamide: hyperuricemia
- Ethambutol: optic neuritis
- Streptomycin: vestibular toxicity

Evaluation Response To Treatment

Response To Anti TB Chemotherapy is Best Evaluated Through Sputum Examination

After 2 Months of Therapy 85% of Patients = Sputum negative

2 negative sputum must be present before stop treatment !!

Some more !?

LTBI vs. pulmonary TB disease

■ Latent TB Infection

- ❑ Tuberculin skin test (TST) positive
- ❑ Negative chest radiograph
- ❑ No symptoms or physical findings suggestive of TB disease

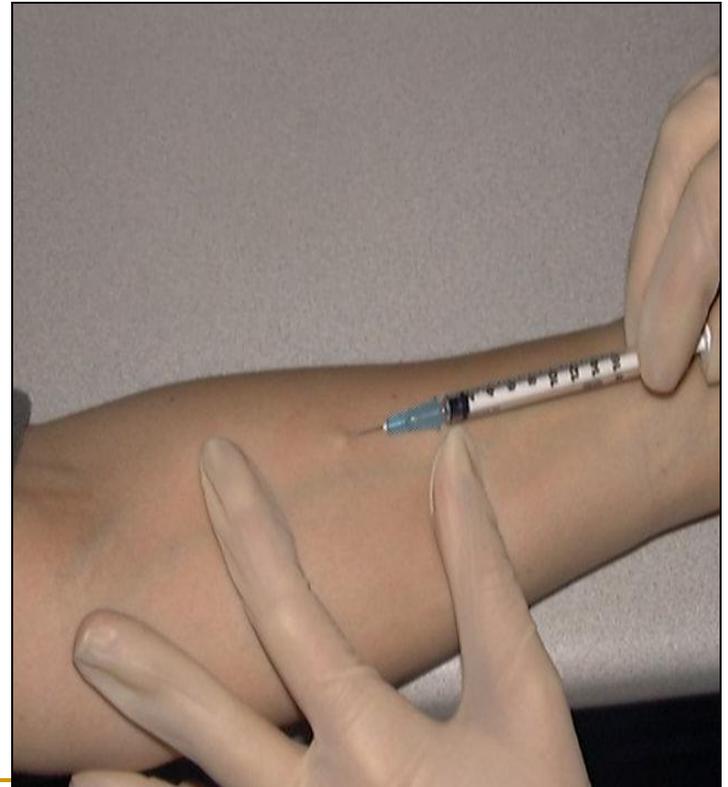
■ Pulmonary TB Disease

- ❑ TST usually positive
- ❑ Chest radiograph may be abnormal
- ❑ Symptomatic
- ❑ Respiratory specimens may be smear or culture positive

Administering the Tuberculin Skin Test (TST)

- Inject 0.1 ml of tuberculin intradermally
- Produce a wheal 6-10 mm in diameter

Mostly used on latent TB infection



Tuberculin Skin Test Reading

- The test is read after 48-72 hours by a trained health care worker
- Diameter of the induration (firmness) is measured in millimeters (mm)
- Erythema (redness) is not measured



Inactive (Latent)TB Infection

- LTBI- asymptomatic state in people infected with *MTB*
 - Live, inactive TB organisms are “walled off” inside the body by the immune system
 - Person with LTBI doesn't feel sick & is not contagious, but they may have abnormal CXR
 - TB can reactivate & begin to multiply at anytime after the initial infection (this may occur decades later)
-

Latent TB Infection (LTBI)

- For adults with untreated LTBI & intact immunity the estimated risk of developing active TB is 5% - 10% over a lifetime (50% of those in 1st 2 yrs after infection)
 - With HIV co-infection risk is 5%-10% per year
 - Infants under a year have a 25% - 40% likelihood
 - Adolescents & elderly also at higher risk
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Latent TB Infection

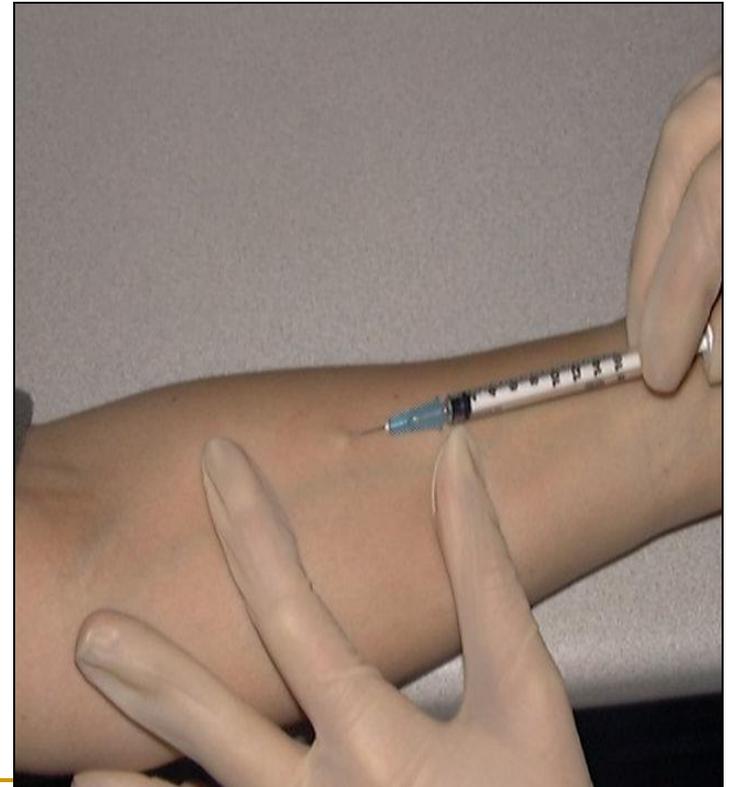
- Evaluate persons for risk factors
 - Test those with a risk factor using the TST or Interferon-gamma release assay (IGRA)
 - Evaluate those with a (+) TST or IGRA by doing a symptom history and chest X-ray
 - Refer to PCP or local public health for treatment recommendations and medication administration
-

Diagnosing LTBI especially patient starting TNF treatment

- The Mantoux tuberculin skin test (TST) is the most common method
 - A TST reaction can take 3-12 weeks after TB infection to become positive
 - A negative TST in a symptomatic patient does NOT rule out TB
-

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TST for LTBI Diagnosis

Criteria for a Positive Reaction

≥5 mm

HIV infection

Contact to
active TB case

Abnormal CXR

Immunosuppression

≥10 mm

Recent immigrants

Injection drug users

Children

High-risk medical
conditions

Residents and employees
of jails/nursing homes,
hospitals

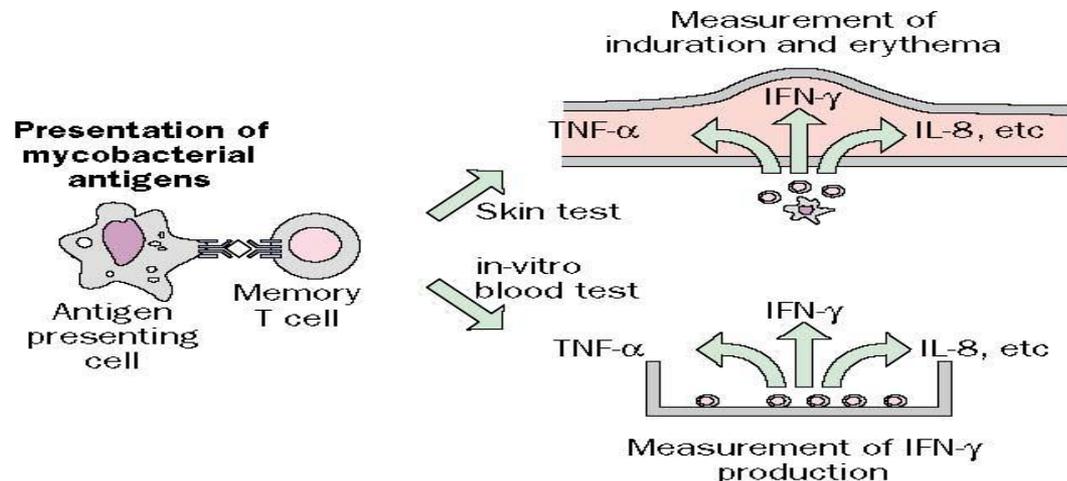
≥15 mm

No risk

Note: Skin test conversion is an increase of ≥10 mm within a 2-year period

Interferon-gamma Release Assays

- Blood test for detecting TB infection
- Requires 1 visit (TST requires 2 visits)
- Results less subject to reader bias and error
- More specific with less cross-reaction with non-tuberculosis mycobacterium and BCG than the TST



Thoughts

- IGRAs are the preferred test in:
 - BCG vaccinated
 - Persons unlikely to get a TST completed
- Implementing IGRAs requires careful thought about logistical hurdles but can be done
- IGRAs may be less accurate (i.e. specific) in low risk populations than previously reported
- Additional longitudinal data is needed in all populations to understand the true implications of a positive test

Recommended Treatment for Latent TB Infection

- INH daily for 9 months
 - or
 - Rifampin daily for 4 months
-

Risk Factors for Progression

- **HIV**
 - **Fibrotic CXR c/w prior TB**
 - Immunosuppression (transplants, TNF-alpha inhibitors)
 - Recent close contact to active TB
 - **Diabetes**
 - **Chronic renal failure**
 - Silicosis
 - Leukemia / lymphoma
 - Head/neck cancer
 - Wt loss > 10%
 - gastric bypass surgery
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