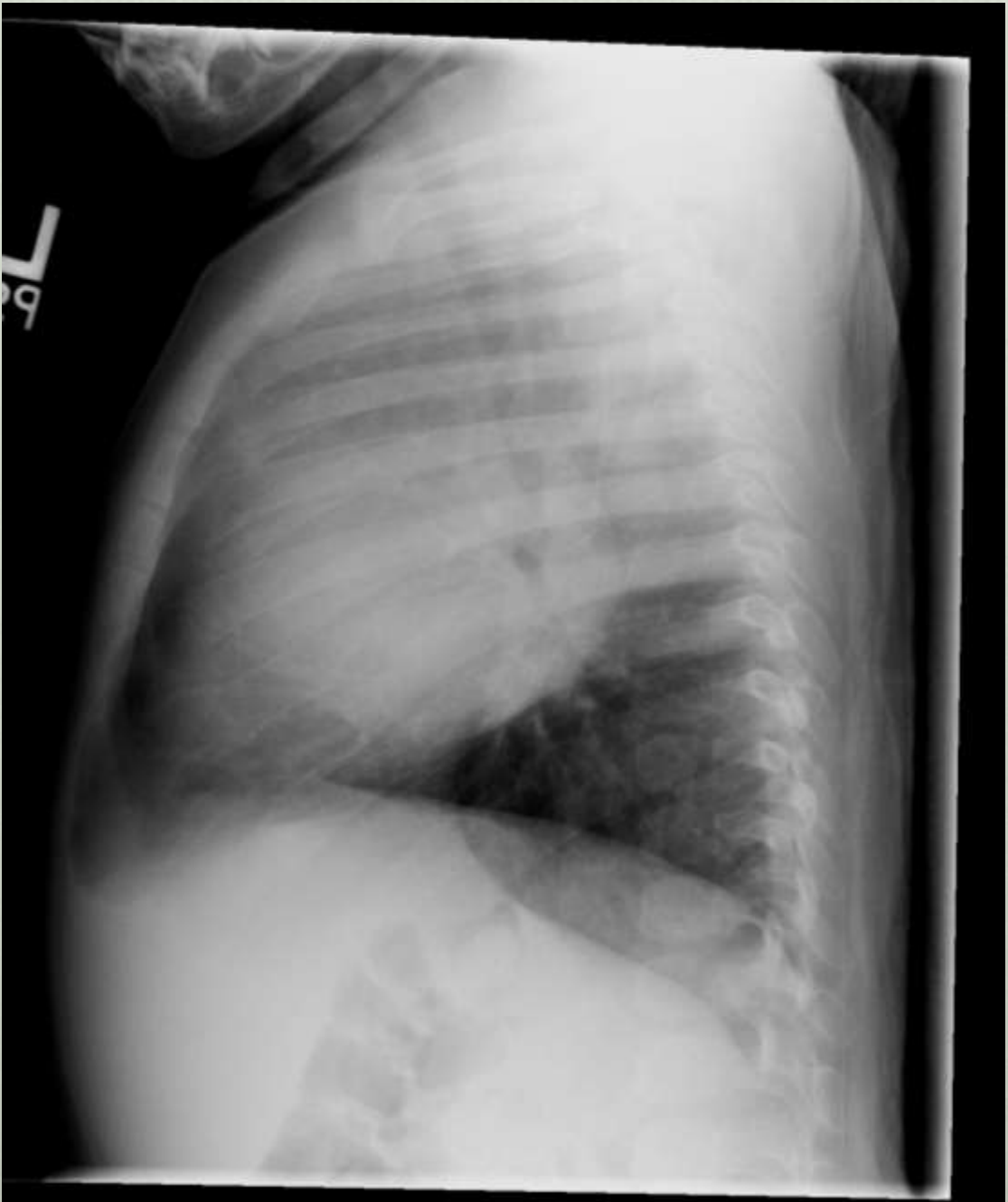
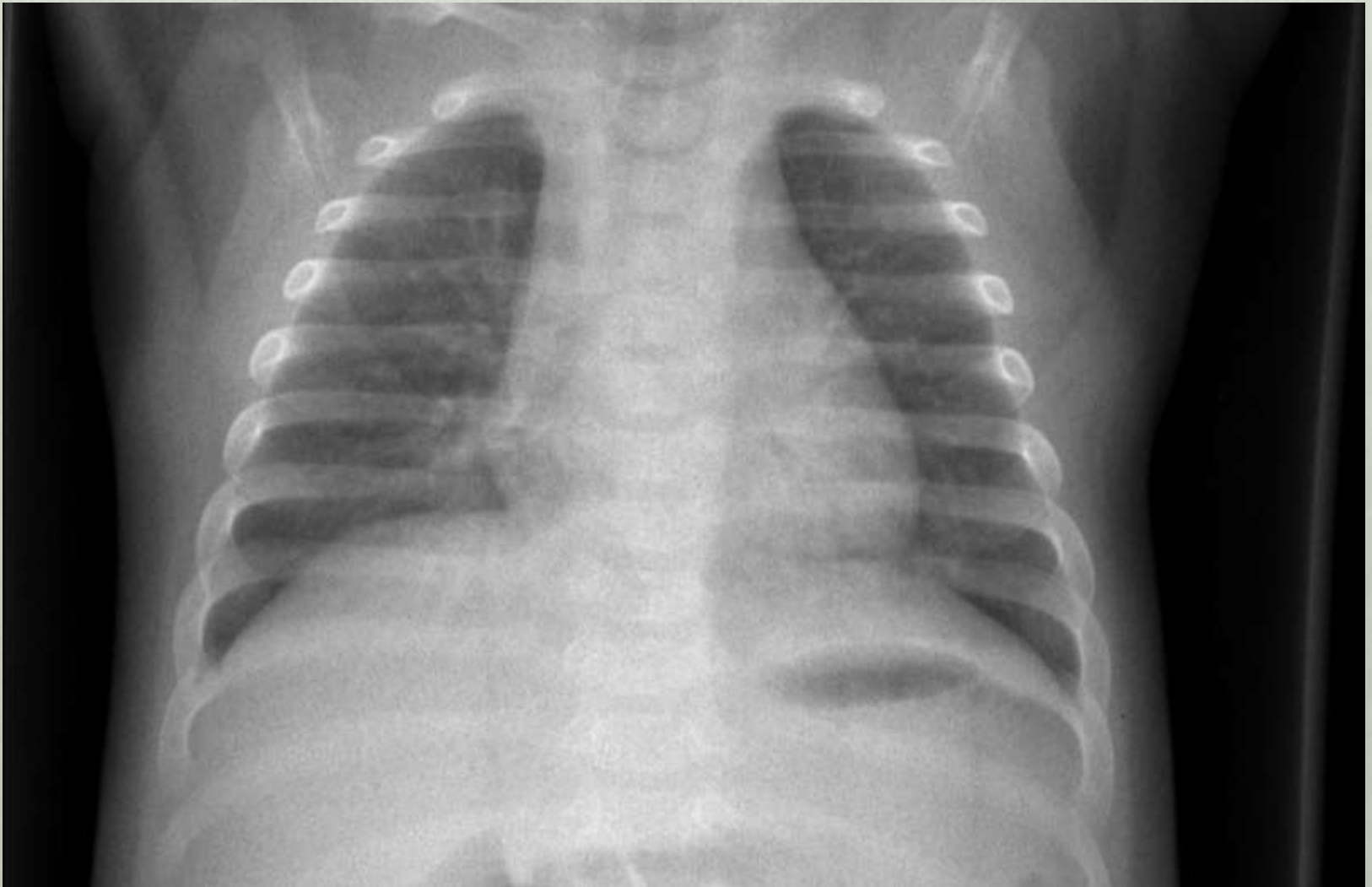


**9 month old with stridor, cough,
low-grade fever, mild hypoxia**







3 months of age – CXR normal

Scenarios:

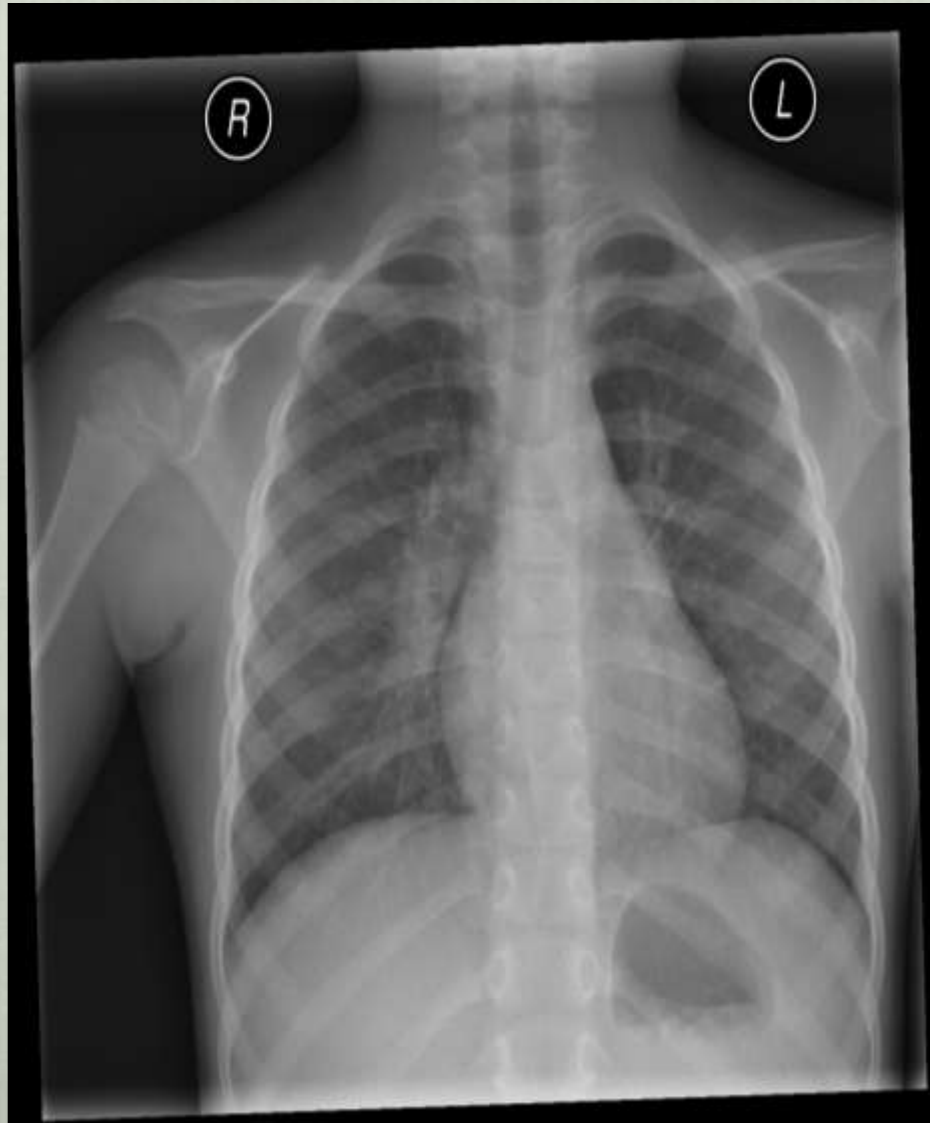
- **Pregnant woman with + PPD**
 - **Next steps?**
 - **CXR negative, asymptomatic: treat for LTBI after delivery (INH x 9 mos). May wish to confirm with T-Spot (IGRA)**

Tuberculosis

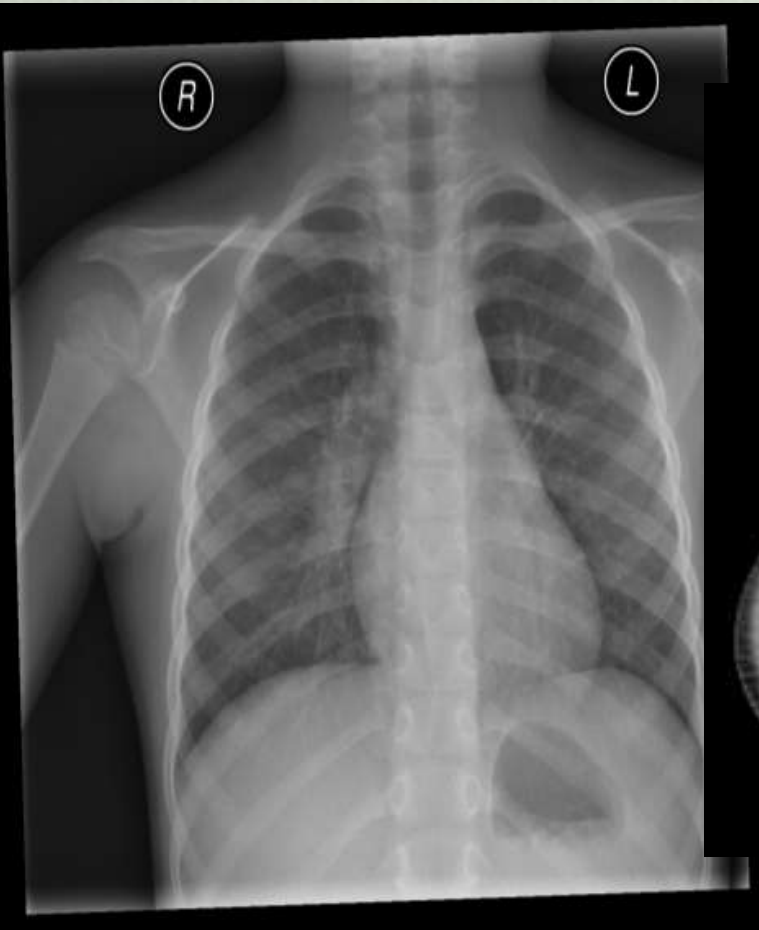
Stephen J Swanson, MD
HCMC Dept of Pediatrics
2013



**6 year returning traveler with mild cough
(Ethiopia x 3 mos)**



**6 year returning traveler with mild cough
PPD+ 18mm**



MYCOBACTERIOLOGY

- **Non-motile, nonspore-forming, weakly Gram-positive rods; often appear bent or beaded**
- **Obligate aerobes**
- **MTB vs NTM, *M. uclerans*, *M. leprae***

Nontuberculous Mycobacteria

- **Termed: Mycobacterium other than tuberculosis (MOTT) , Atypical mycobacterium, Environmental mycobacterium**
- **No evidence for person-to-person transmission**
- **Environmental sources: soil, water, dust, animals**
- **MAI, *M. fortuitum*, *M. kansasii*, *M. scrofulaceum*, *M. marinum***

NTM - II

- **Most common sites: adults – lungs
children – lymph nodes, skin**
- **Granulomas often absent, AFB stains
usually negative**
- **Reaction to PPD variable, usually < 10mm,
waned after months**

Appearance over weeks to months...



Tuberculosis Epidemiology

- **1/3 of world's population infected (~2 billion)**
- **WHO estimate – worldwide:**
 - **~10 million annual new cases**
 - **1.3 – 3 million annual deaths from TB**
- **Poor countries bear most of global TB burden (majority TB cases in Asia/Africa)**
- **~15% of TB cases = HIV+**

Worldwide Burden of Pediatric TB

- **Incidence ???**
- **Prevalence ???**
- **Death Rate ???**
- **Rate of Infection ???**
- **~ 11% of TB disease occurs in children < 15y, with 400,000 annual pediatric TB deaths**

Challenges of *M. tuberculosis* Diagnosis

- **Slow growing mycobacteria**
 - **Replicates every 12-24 hours**
 - **Delay in culture results**
 - **AFB smears not specific for MTB (suggestive)**
- **Requires specialized media & labs for growth**
- **TB drug susceptibility testing (not available overseas)**
- **Pulmonary TB may be AFB smear and culture negative (USA = 10-15% of PTB)**
- **Chronic respiratory conditions common overseas**

Treatment Challenges with MTB

- **Combination Therapy Required**
- **Prolonged Treatment**
- **2nd line TB drugs**
 - **Expensive**
 - **Poorly tolerated**
 - **Less effective**

Transitions in Tuberculosis

Susceptible

Exposed

Infected

Diseased

Sick

Diagnosed

Treated

Cured

Stages of Tuberculosis

Exposure

- **Defined by contact investigation – recent (< 3 months) contact with infectious case**
- **Negative ST, physical exam, CXR**
- **Period during which skin test may be negative in infected person**
- **Children < 5 years old usually treated because disease may develop rapidly**
- **Older children, adults often not treat, but repeat skin test after exposure over**

Stages of Tuberculosis

Infection

- **Hallmark is “positive” PPD**
- **“Germs in the body”**
- **CXR is often normal**
- **No symptoms, physical exam normal**
- **Anyone with infection should be treated when risk of dz outweighs adverse reaction to medication**



Stages of Tuberculosis

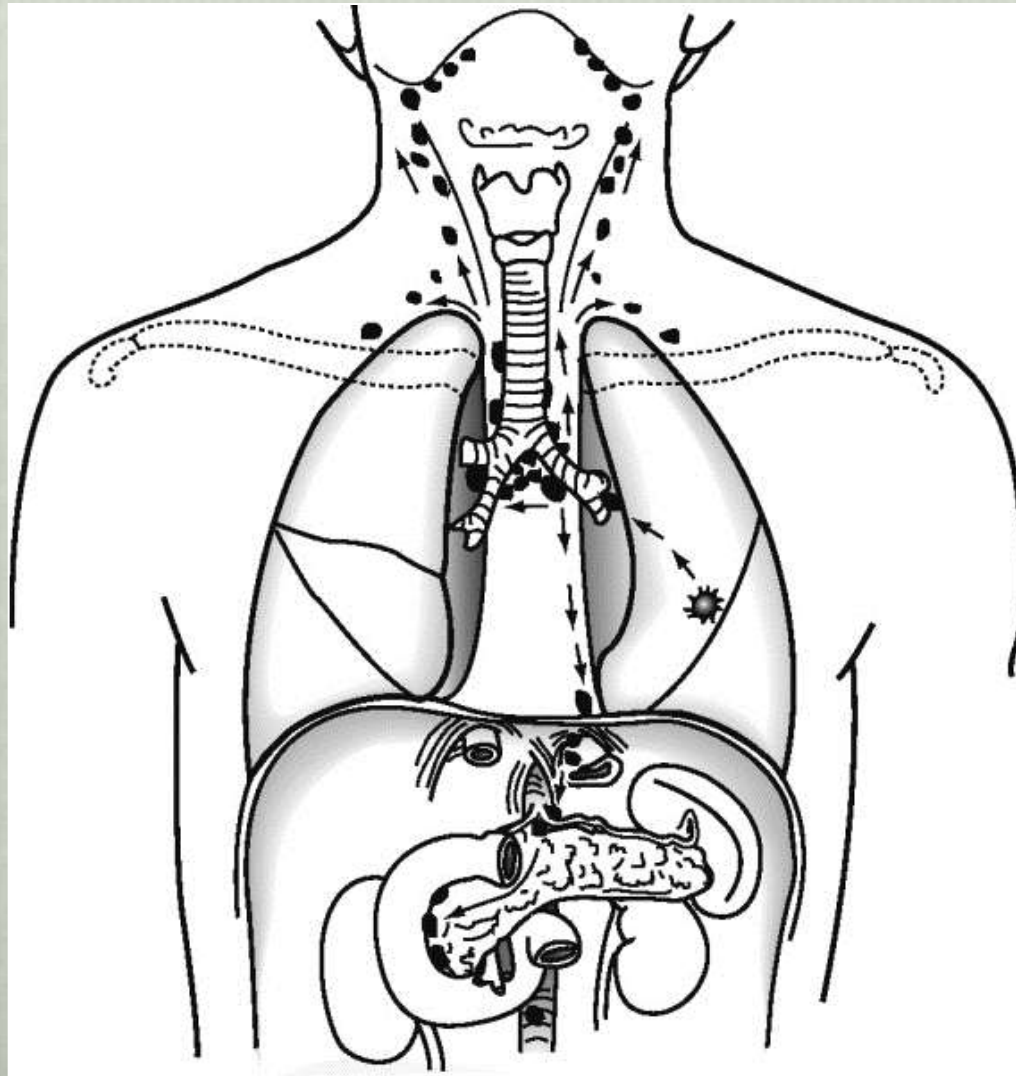
Disease

- **Clinical and/or radiographic manifestations**
- **Primary: complication of initial infection**
- **Reactivation (Postprimary): disease after period of dormancy**
- **TST negative in 10 – 20% of all disease cases (50% of miliary or meningeal diseases)**

Pathogenesis of Tuberculosis

- Lungs are portal of entry in > 95% of cases
- Organisms in droplet land in alveoli
- Infectious dose is unknown
- Organisms are ingested by non-sensitized macrophages; intracellular replication occurs
- Organisms travel to regional lymph nodes via cells; lympho-hematogenous dissemination occurs
- CMI and delayed-type hypersensitivity generally develop in 4 – 12 weeks; if effective, replication is halted and infection remains subclinical

Lymphogenic spread of TB from Primary Pulmonary Focus (LUL)



Age-specific Risk for TB Disease Development following Primary Infection

<u>Age (years)</u>	<u>Risk of disease</u>	
▪ < 1	Pulmonary* 30 – 40%,	TBM or miliary 10–20%
▪ 1 – 2	Pulmonary* 10 – 20%,	TBM or miliary 2 – 5 %
▪ 2 – 5	Pulmonary* 5%,	TBM or miliary 0.5 %
▪ 5 – 10	Pulmonary*¶ 2%,	TBM or miliary < 0.5 %
▪ 10 – 15	Pulmonary 10 – 20%,	TBM or miliary < 0.5%

*Ghon focus and/or lymph node ¶pleural effusion or adult type
TBM, tuberculous meningitis

Adapted from Marais BJ, Gie RP, Schaaf HS. et al. The natural history of childhood intra-thoracic TB – a critical review of the literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004;8:392-402



Skin – Testing, Infection, and Disease

- **TST takes 3 weeks to 3 months to turn positive after infection**
- **Risk of disease after untreated infection**
 - **Normal adults: 5 – 10 % in lifetime; (half of risk in first 2 – 3 years)**
 - **HIV – infected adults: 5 – 10% per year**
 - **Infants: 40-50% in initial 1 – 2 years**
 - **Older children (5 – 15 years): 2 – 10%**

TST (PPD)

- False Negative?
- False Positive

TST (PPD)

▪ False Negative?

- Window Period
- Extremes of age (neonate, elderly)
- Steroids
- Co-occurring viral infections (i.e., influenza)
- Recent live vaccines
- HIV
- Malnourished
- Extrapulmonary/miliary TB
- Improper Technique
- Inexperienced reader
- Reader Bias
- And for no explanation!

▪ False Positive

- BCG
- Environmental NTB
- Allergic reaction to components (peaks at 24 – 48h)

Induration Size = Positive TST

≥ 5 mm

- HIV coinfection
- Immune compromise
- Recent contact to infectious TB case
- Abnormal CXR, suspected dz

≥ 10 mm

- Foreign borne, high-risk country
- Drug user
- HR congregate setting
- Children < 4 years

No risk factors: ≥ 15 mm

BCG Vaccines

- **Negligible effect on TB epidemiology**
 - **Does not prevent infection**
 - **Little effect on reactivation disease**
- **Major use is to prevent life-threatening forms of TB in infants and children**
- **Most studies, 80-90% of PPD reactivity lost within 5 years after newborn BCG vaccination**

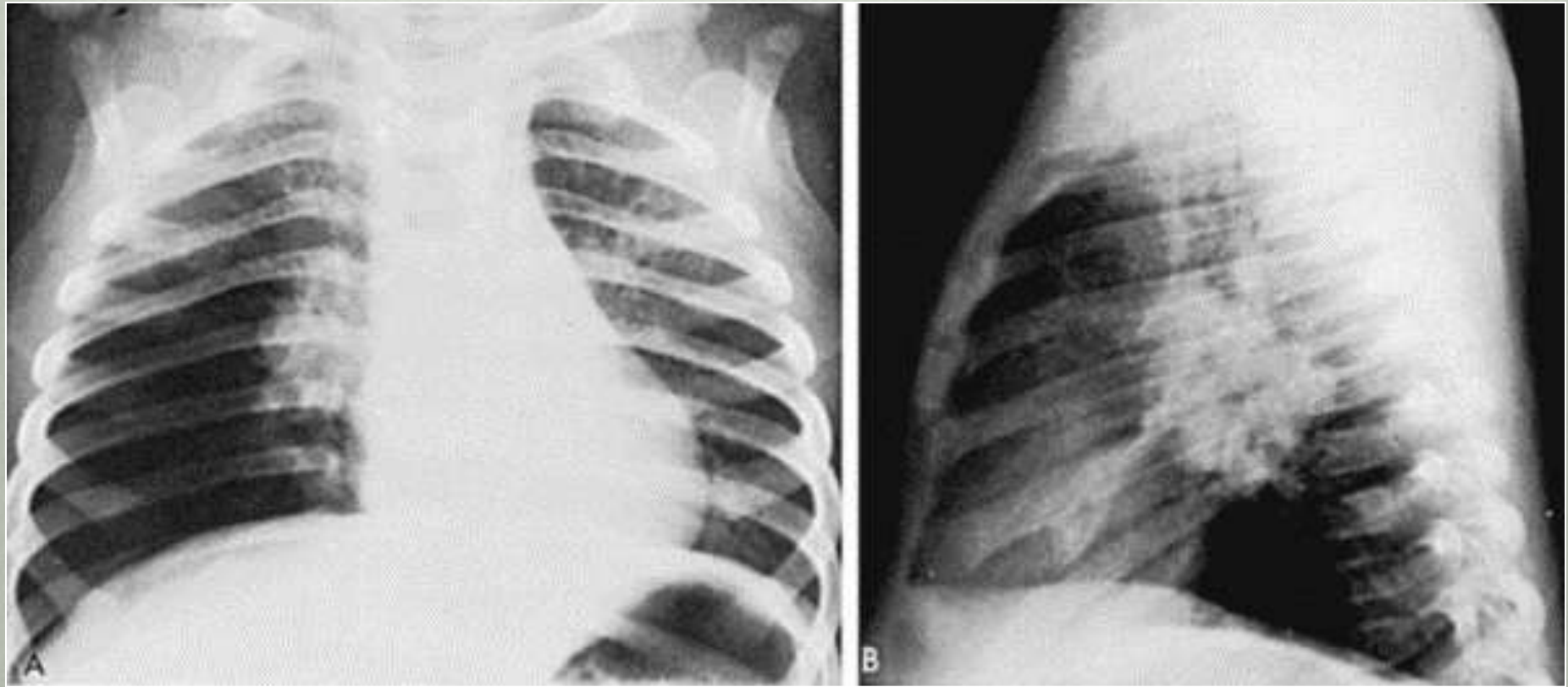
Interferon- γ Release Assays

- Detects IFN- γ after lymphocyte stimulation with MTB proteins
- More specific than TST, equal sensitivity
 - Not influenced by NTM, BCG
- Lower IGRA sensitivity in immunocompromised
- May be more sensitive in recent infection
- Not well studied in young kids (< 4 years)
- Preferred test in older kids, refugees/immigrants

Clinical and Radiographic Manifestations of Childhood Pulmonary TB

- Paucity of signs and symptoms relative to CXR findings
 - In U.S., up to 50% children with pulmonary TB have few or no symptoms
- Infants more symptomatic: fever, cough, focal wheezing, respiratory distress
- Predominance of hilar and/or mediastinal adenopathy (not always seen on plain film)
- Any lobe of lung involved; 25% multilobar
- Local pleural reaction/effusion is common
- Collapse – consolidation or segmental pattern most common
- Obstructive signs/symptoms with endobronchial lesions
- Not contagious

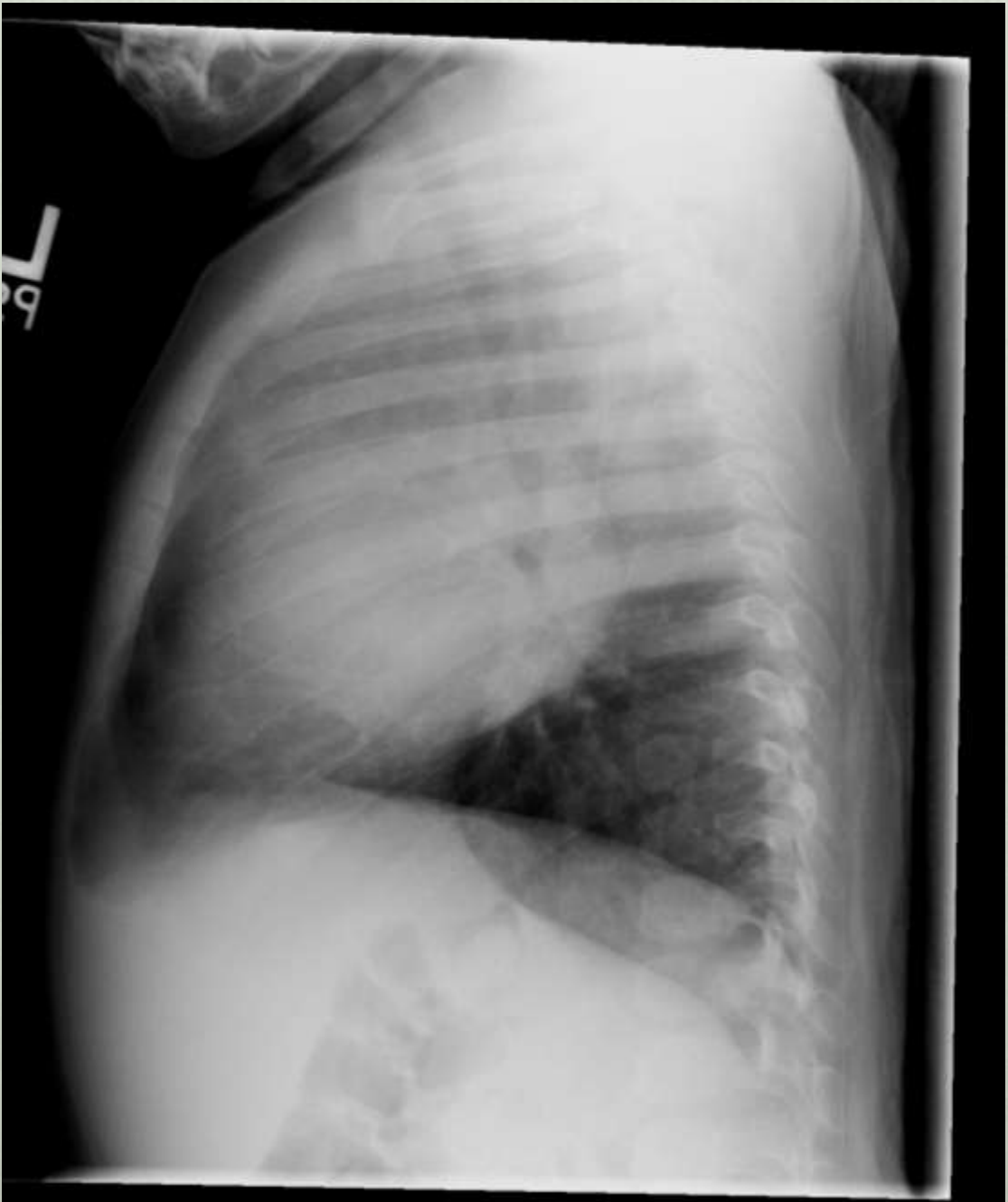
**8-month-old girl with obstructive
hyperaeration of the right lower lobe,
large hilar nodes compressing RLL bronchi**



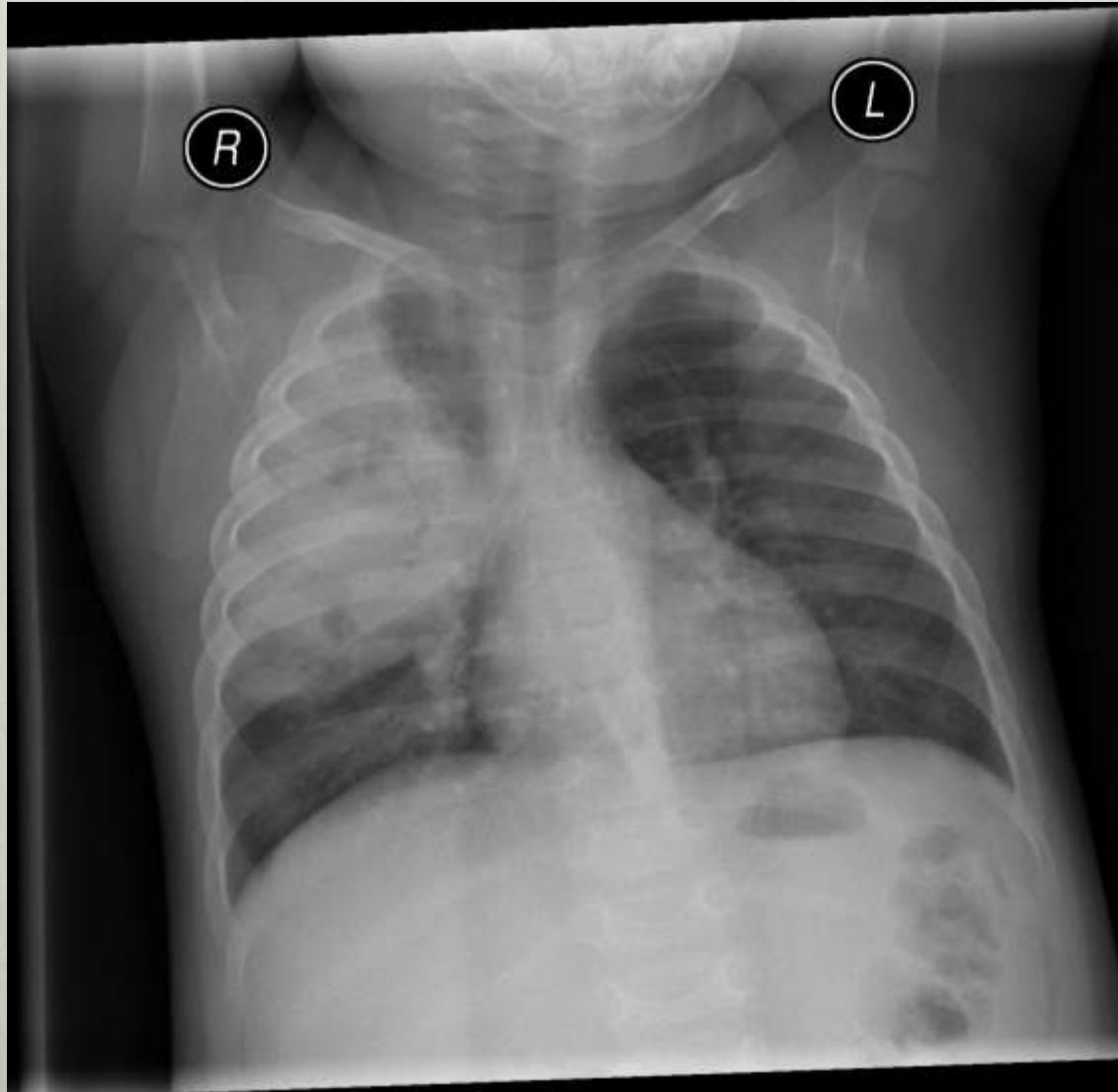
**TB should be considered in patients with hyperaeration of
unknown etiology**

9 month old





2 months later – on 4 drug therapy



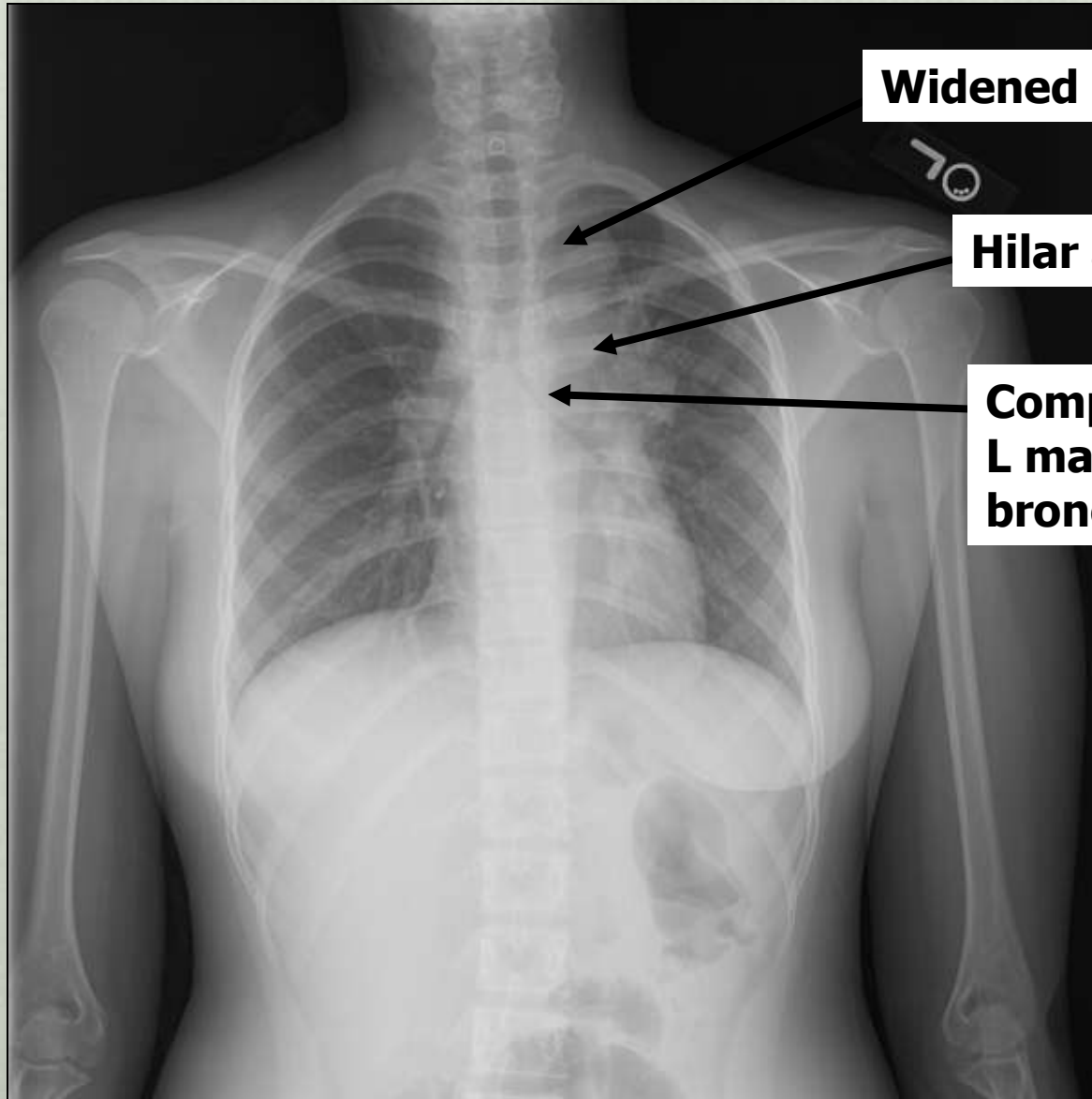
**RUL pulmonary TB,
Subcarinal node, bronchial obstruction**



Fever and Cough in 12 year old



12 year old CXR



Widened mediastinum

Hilar adenopathy

**Compression of
L mainstem
bronchus**

Sept 2006



Dec 2006

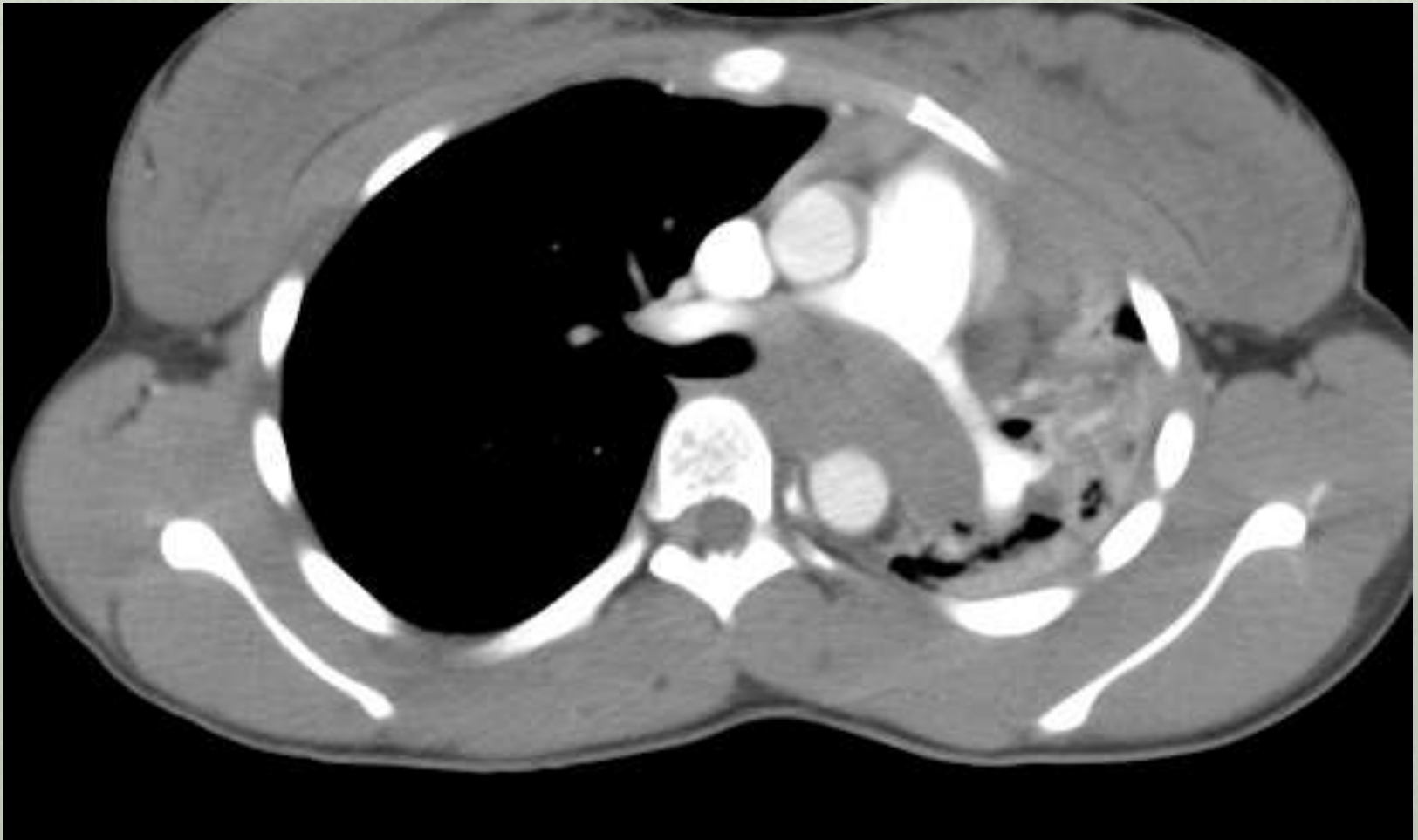


Aorticopulmonary Node

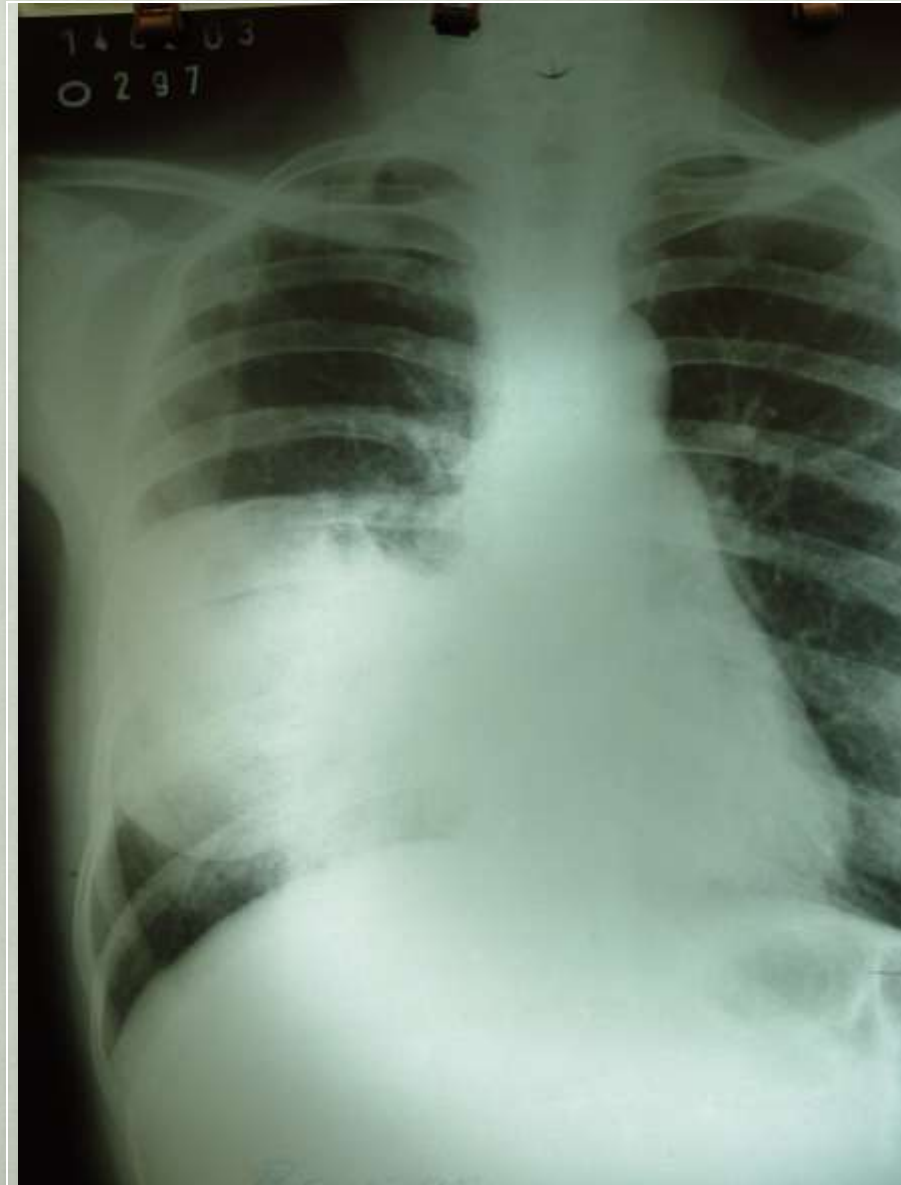


Subcarinal Node

L Mainstem compression



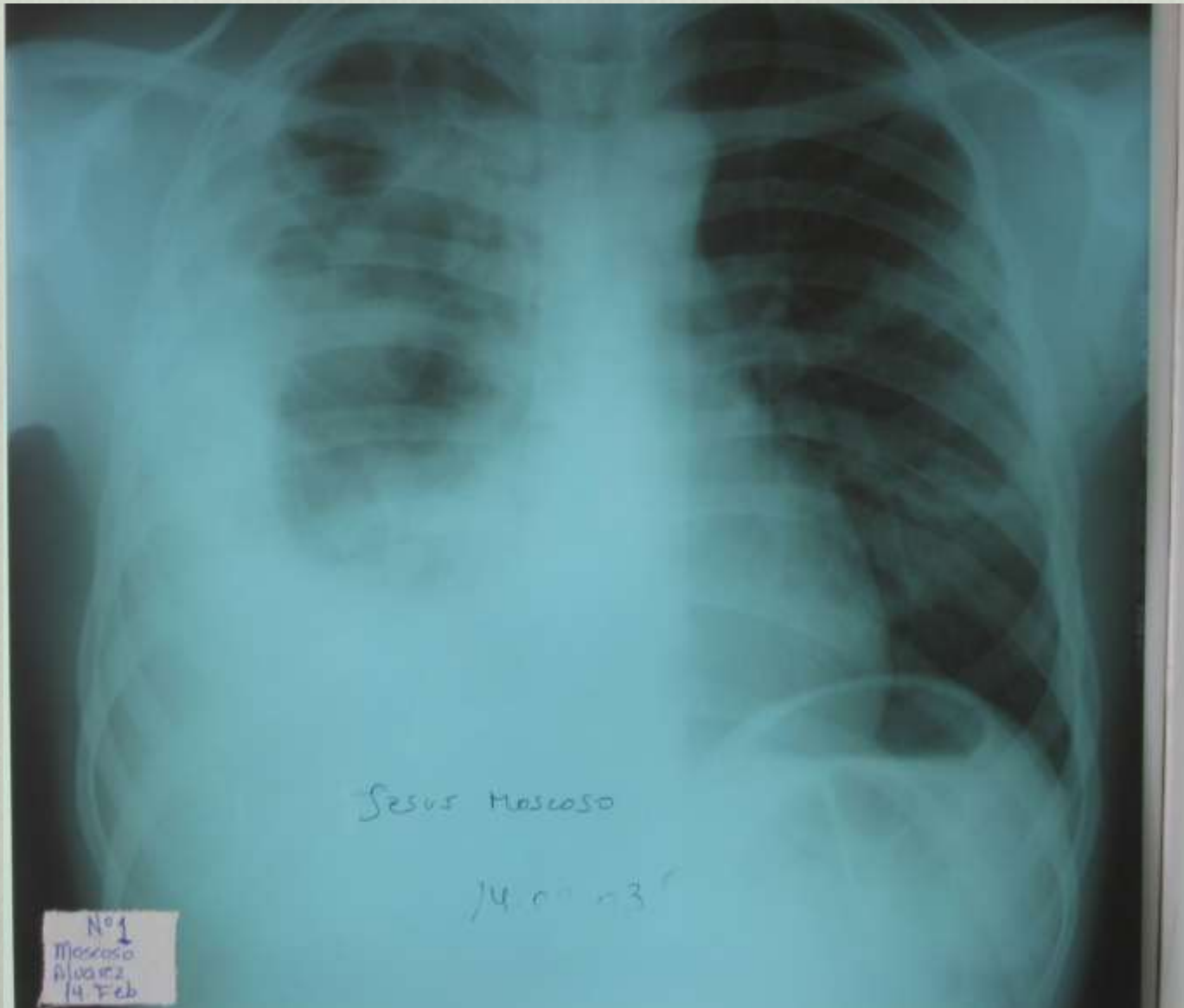
RML Syndrome

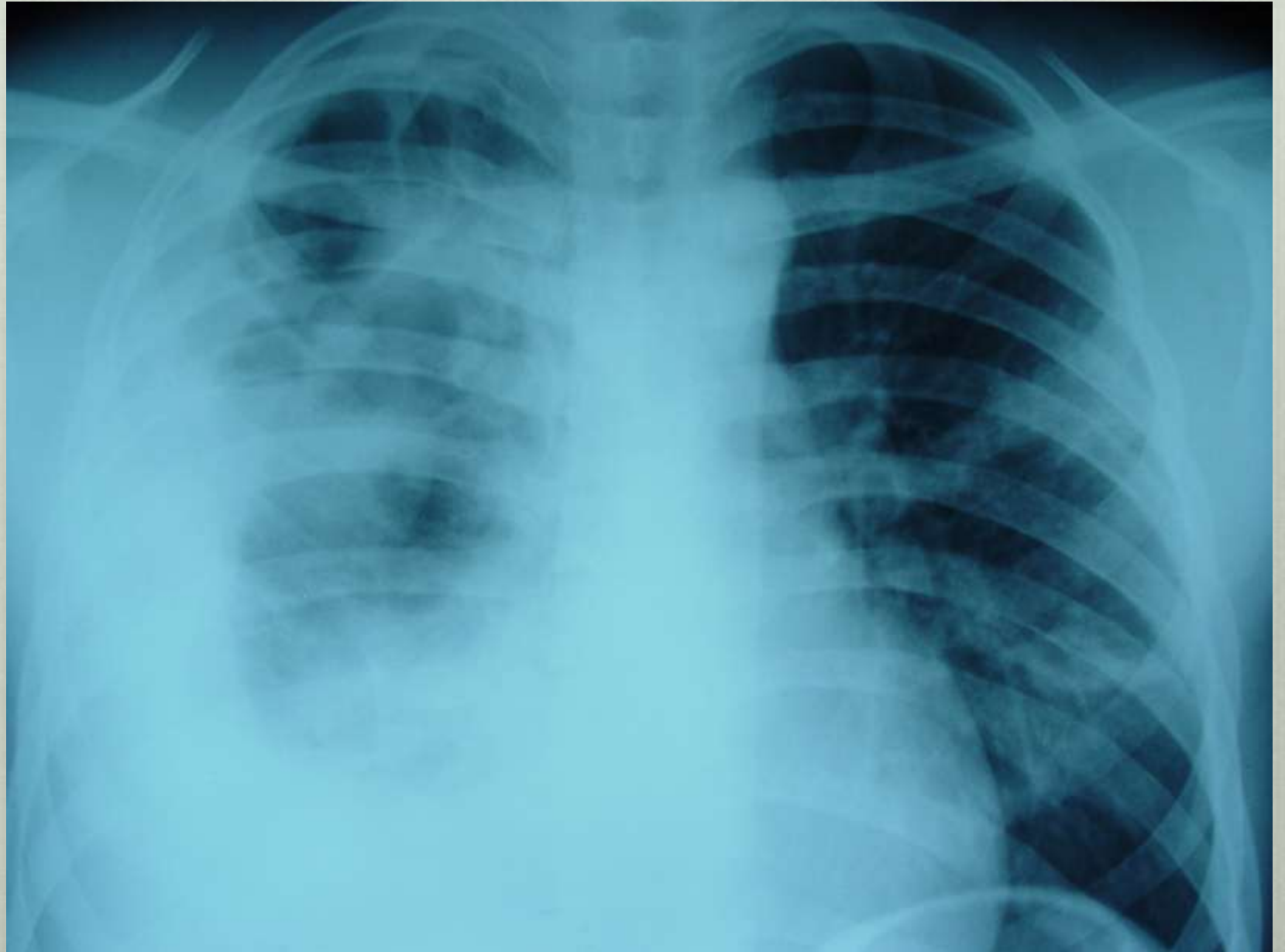


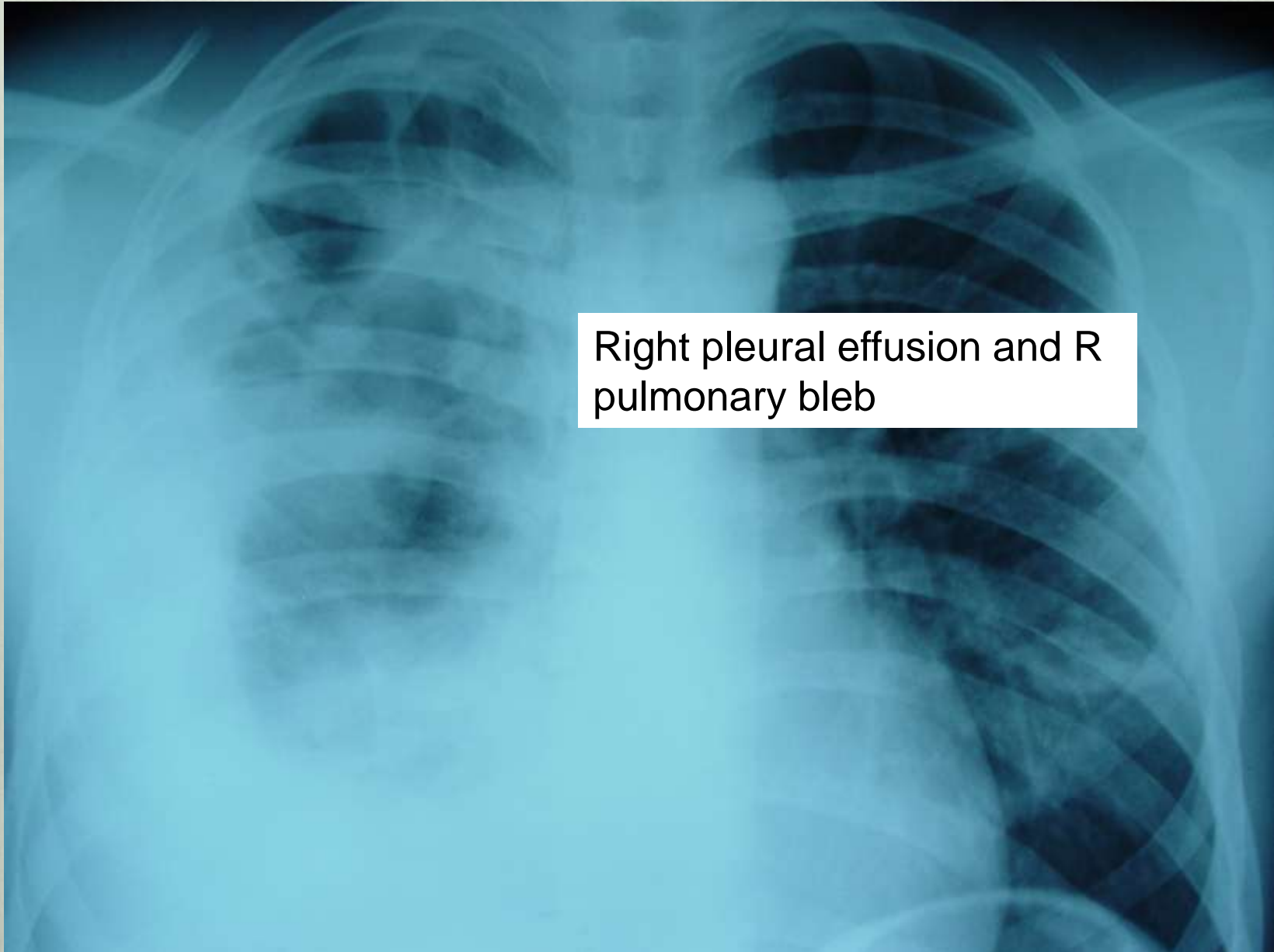
RML Syndrome - TB



14 yo with PTB: 2 findings







Right pleural effusion and R pulmonary bleb

1 year old with pulmonary TB

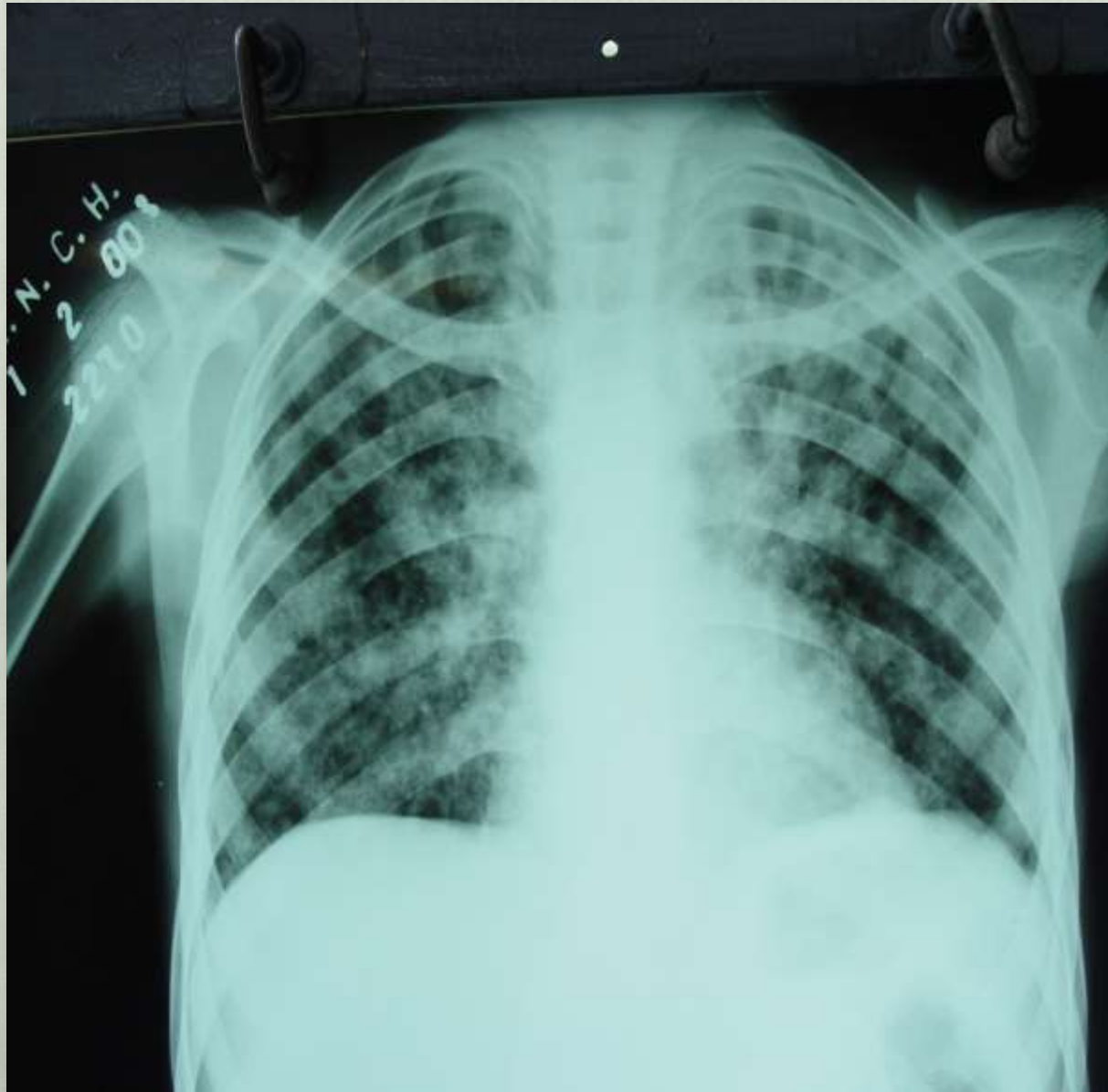


Pulmonary TB





School age boy CXR



Cambodian 4 year old



When to suspect TB in kids

- **CXR much worse than clinical picture**
- **Wheeze, cough not responsive to albuterol**
- **Failure to thrive, reduced playfulness**
 - **Don't expect fevers, night-time sweats, significant cough, upper lobe (reactivated) disease, or +PPD in pediatric TB cases**

Diagnosis of TB in children

- **Clinical/epi: gold standard**
- **AFB stains: positive < 10% of cases**
- **AFB culture: 3 early a.m. gastric aspirates**
 - **All children: 20 – 40% of cases**
 - **Infants: up to 75% of cases**
 - **CSF, pleural fluid: ~25% of cases**
- **PCR: ? Sensitivity, specificity 80-90%**

Diagnosis of TB adults

- **Proper sputum collections**
 - **Best collected in early AM**
 - **2nd sputum smear increases AFB smear yield by 13%**
 - **3rd sputum smear – 4%**
 - **At least 2 quality sputa samples recommended (3 in settings where TB culture not readily available)**

Complications of Primary Childhood Pulmonary TB

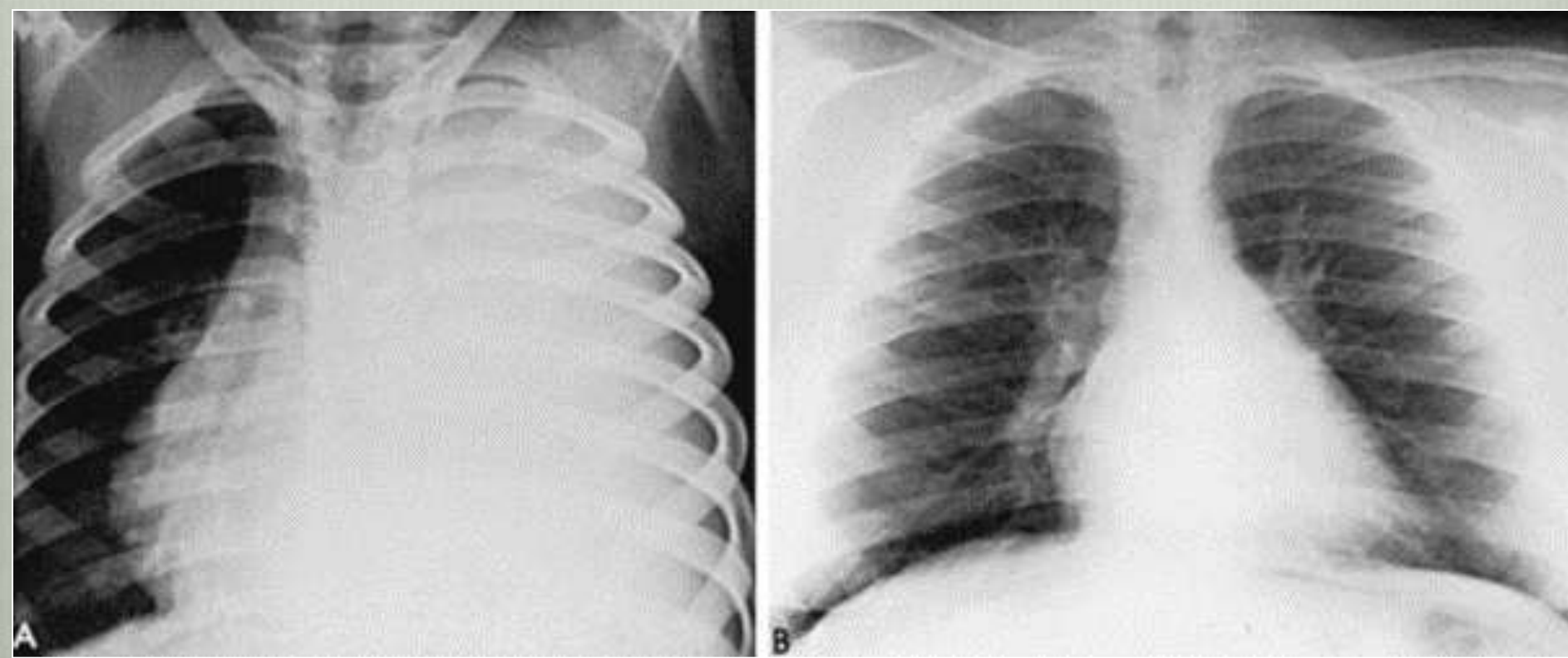
- **Progressive local disease – cavitation**
- **Obstructive emphysema**
- **Pericardial or esophageal perforation from subcarinal nodes**
- **Sudden death – asphyxia, bleed**
- **Bronchiectasis**
- **Calcification – takes at least 6 months**

TB Pleural Effusion in Pediatrics

- **Primarily adolescents**
 - **uncommon before age 5, rare before age 2**
- **Usually unilateral, can be bilateral**
- **Rare in miliary disease**
- **Usually abrupt onset: fever, chest pain, SOB**
- **Thoracentesis: several hundred WBCs, high protein, glucose < 39, AFB negative, culture positive 30-60%**

**5-year-old boy with massive left pleural effusion
caused by tuberculosis.**

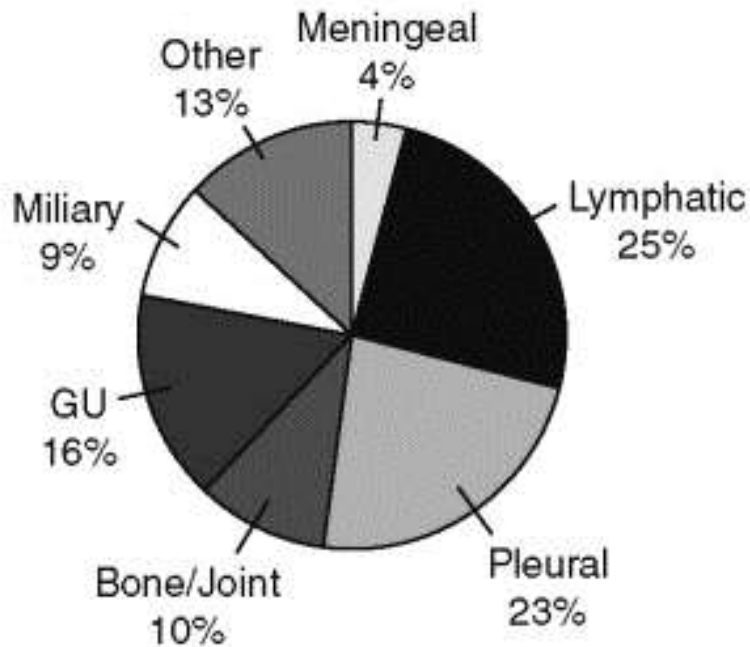
**B: Patient 6 years later with a normal chest film
and no physical complaint**



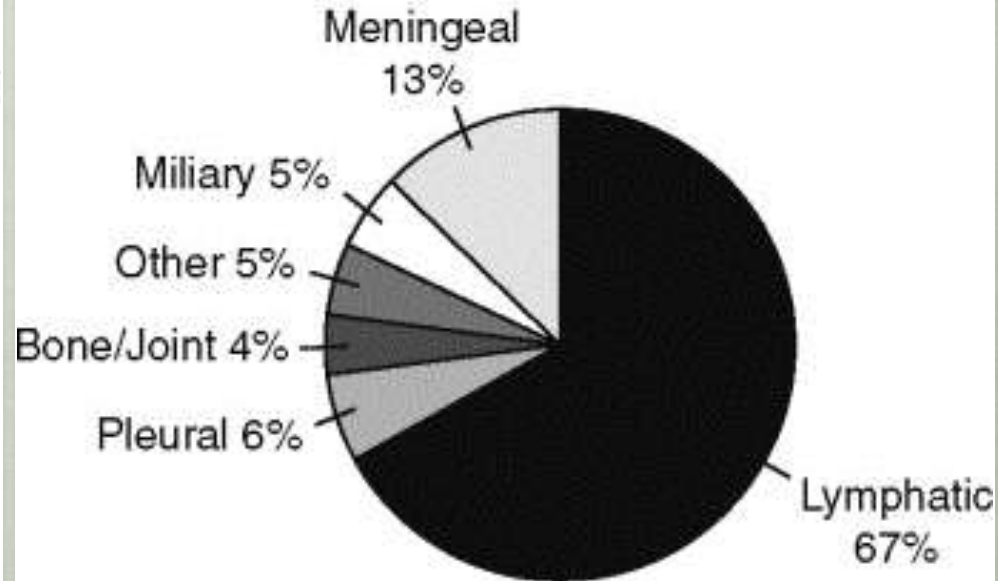
Extrapulmonary Tuberculosis

Extrapulmonary disease by site in adults and children

Extrapulmonary cases in adults



Extrapulmonary cases in children
<15 years of age



Miliary (Disseminated) TB in childhood

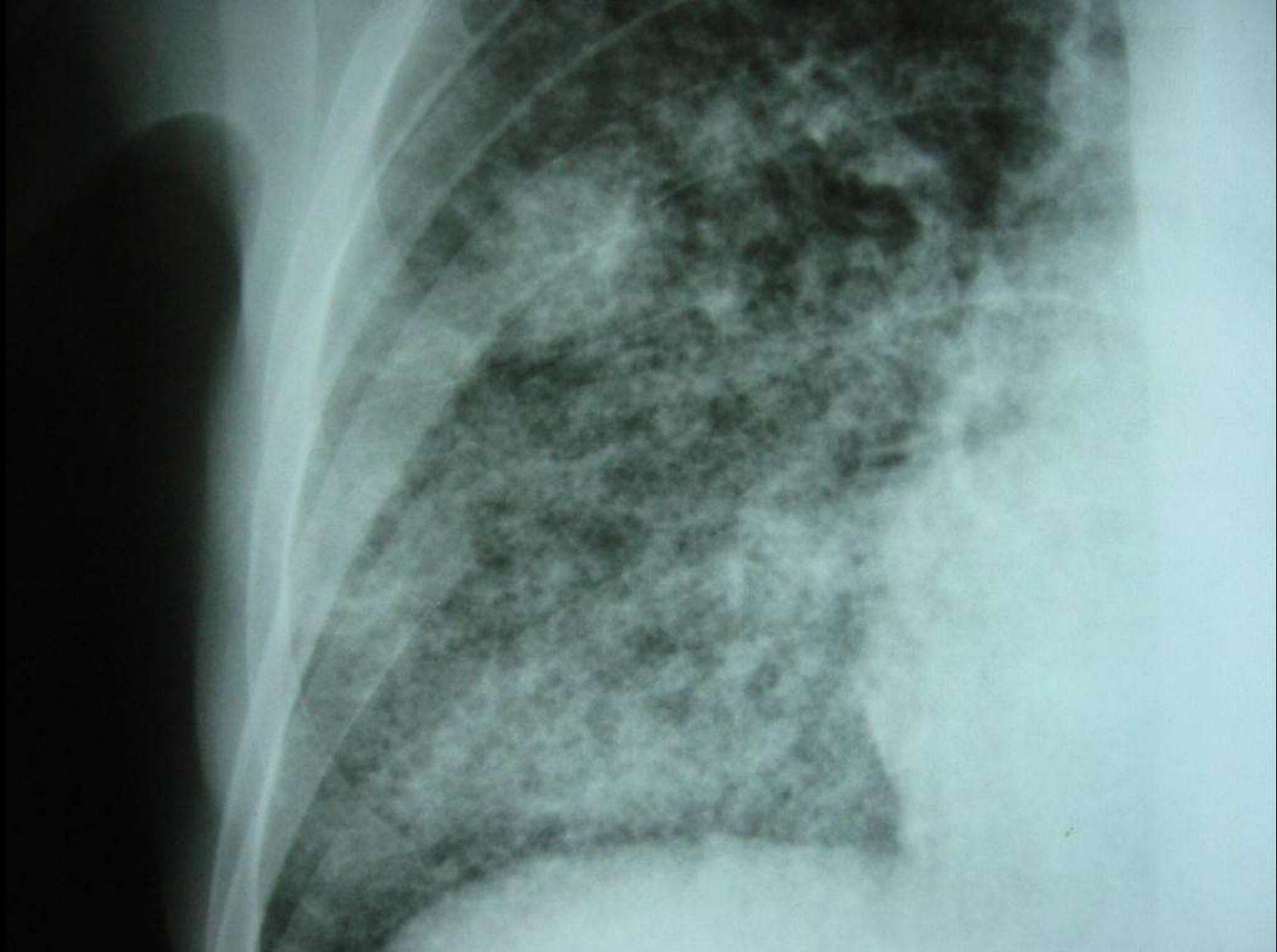
- **Early complication of primary infection**
- **1-2 mm opacities, aggregates of macrophages, lymphs w/ necrosis**
- **Most common in infants, recent after infection**
- **Protean manifestations – FUO common, rapid breathing, wt loss**
- **Insidious or explosive presentation**
- **CXR usually normal initially, then classic. LUNGS CTA!**
- **TST negative 50%**
- **Other findings: HSM, LAD, cutaneous**
- **Dx: gastric aspirate, bronchoscopy, bone marrow, urine cx**

Miliary TB = extrapulmonary TB!

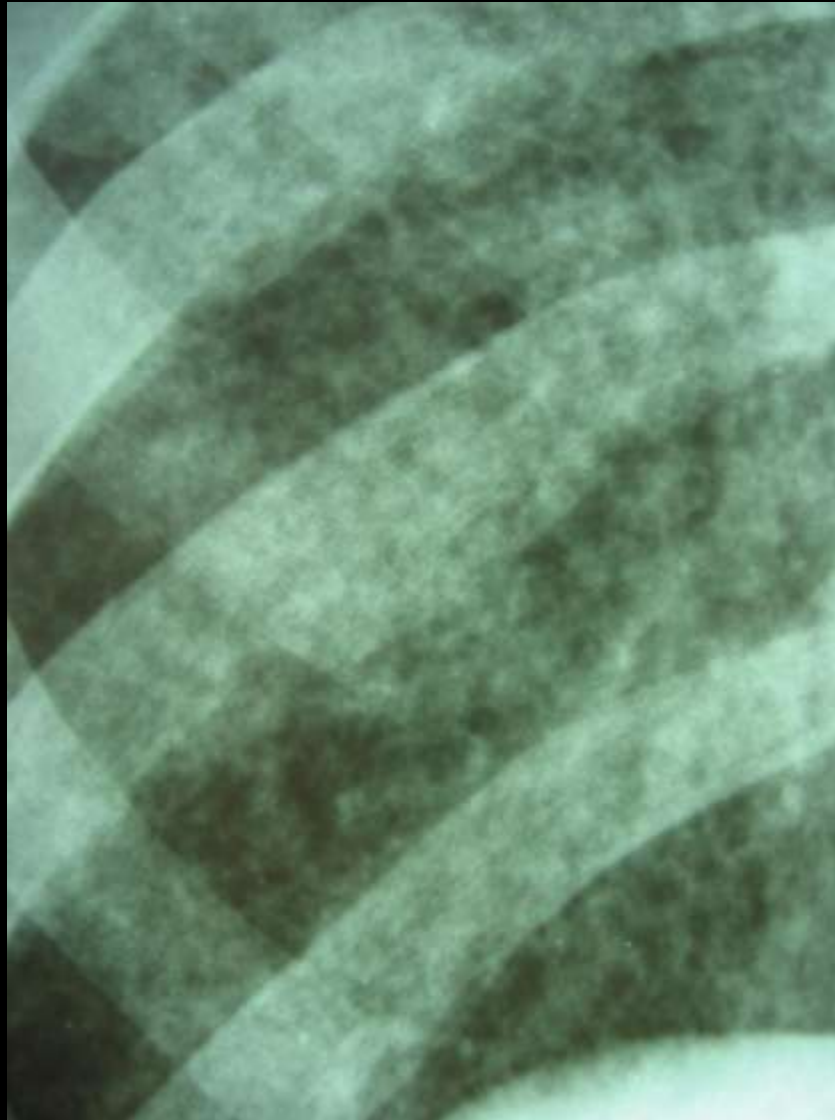


Miliary TB:

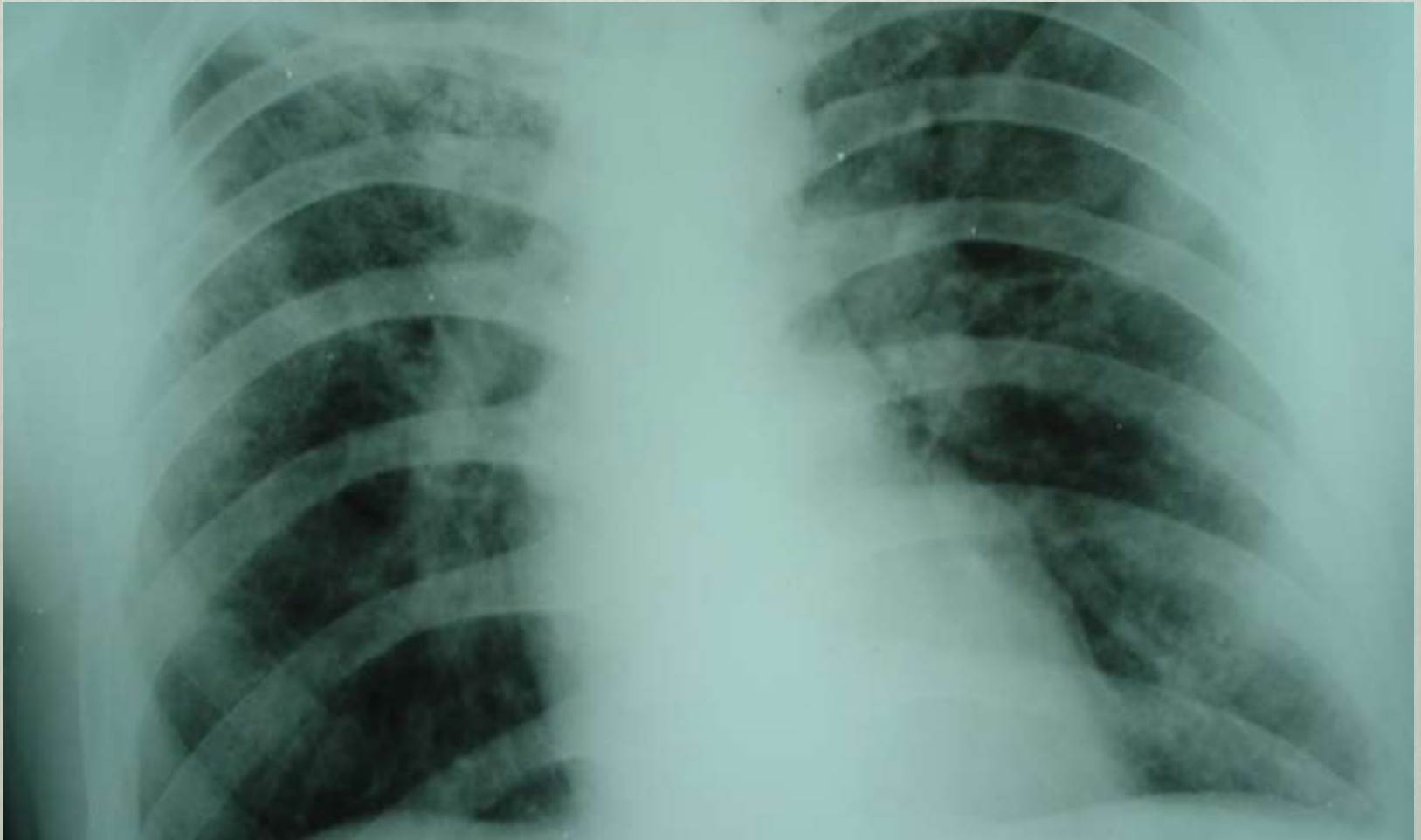
1-2 mm rounded opacities throughout all



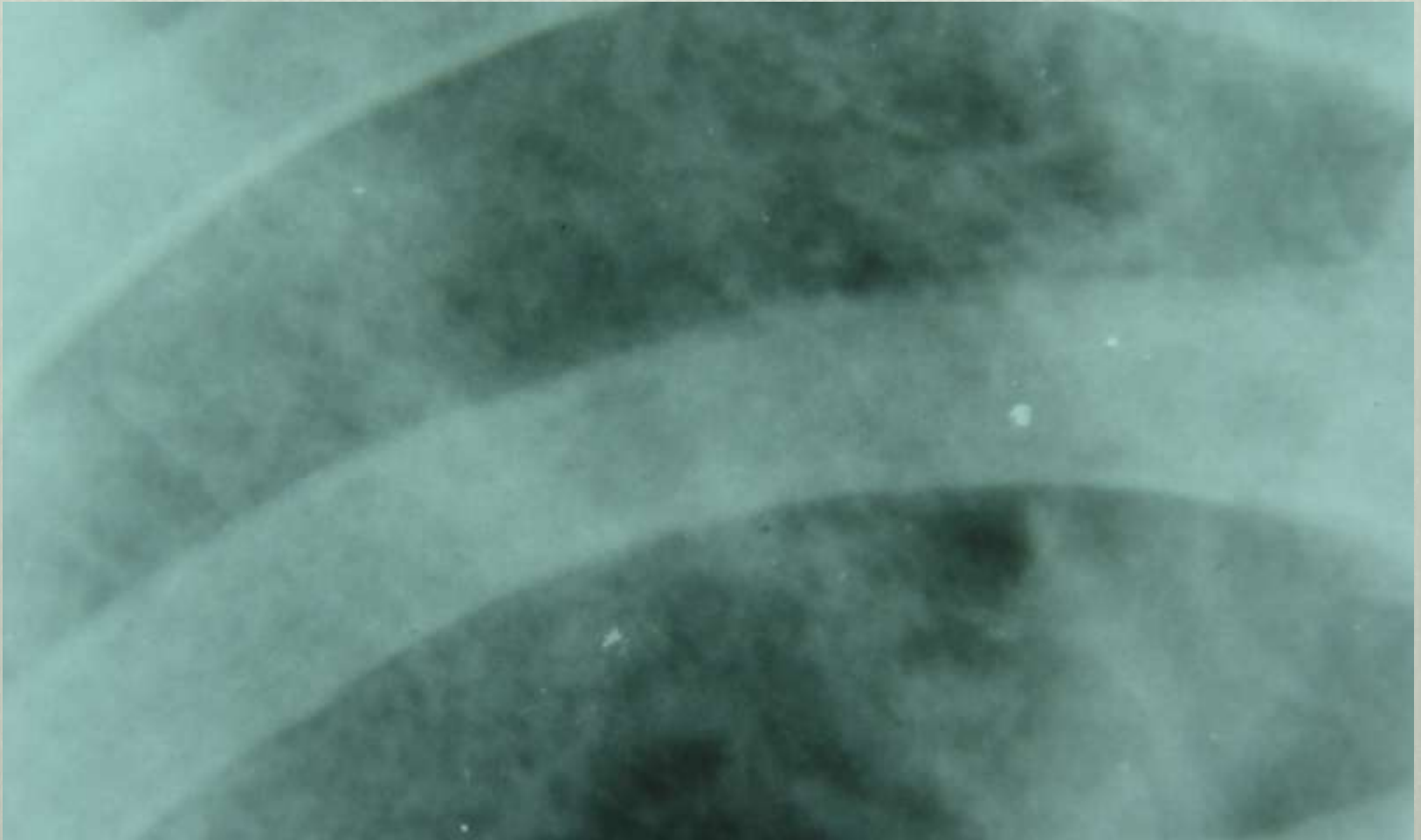
Miliary TB



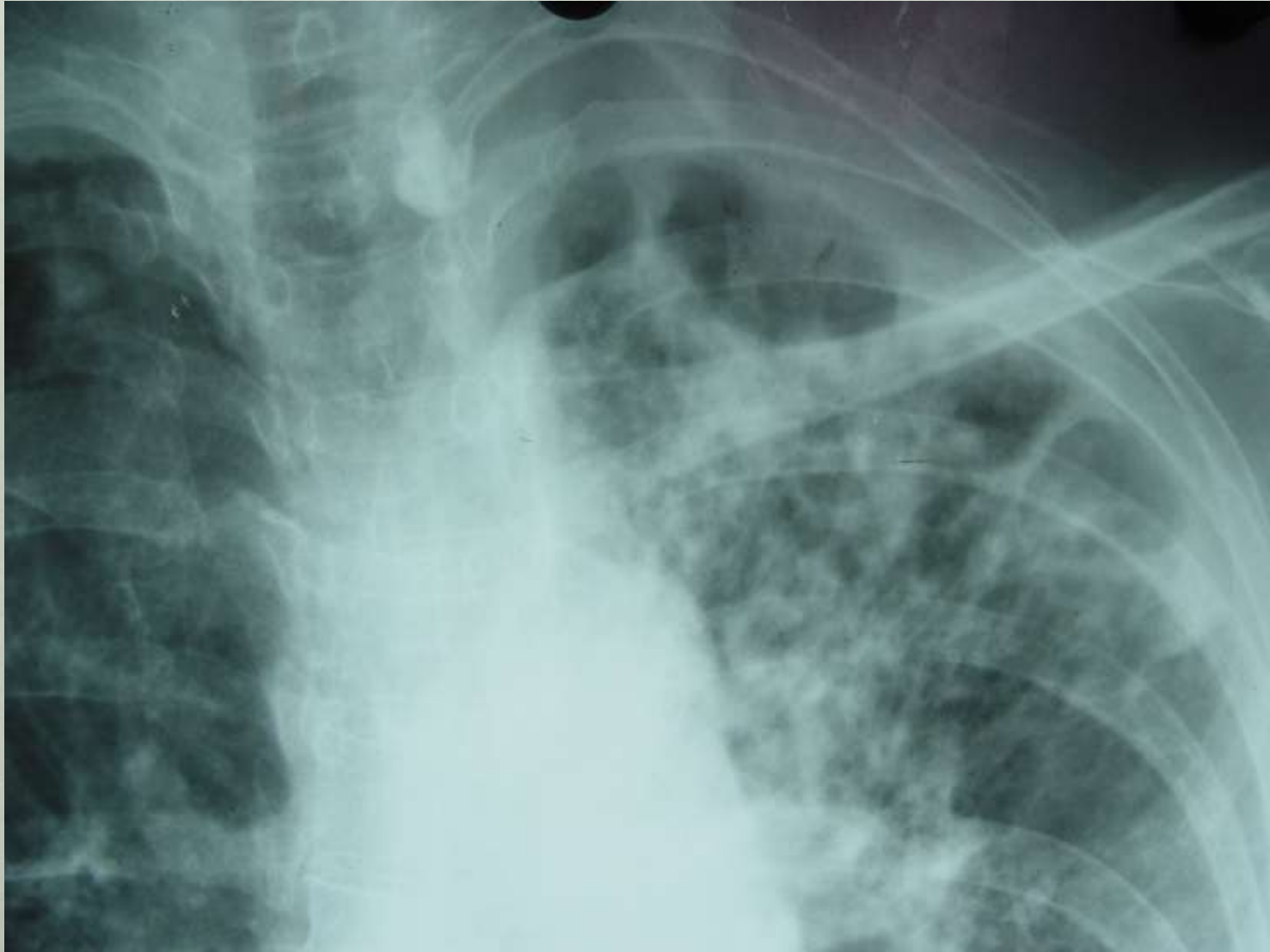
Miliary TB



Miliary TB – Up close



Multiple Bullae, Pleural Thickening



Lymphadenitis Caused by MTB

- Most often unilateral; may be bilateral
- CXR usually normal
- Usually indolent onset of enlarged, fixed, matted nodes in anterior chains, submandibular
- Submental, occipital, axillary, supraclavicular nodes less often
- Absence of systemic findings, minimal tenderness
- Often progress, “break down” with sinus tracts
- Major Ddx: NTM, malignancy





Weeks to months...



NTM vs TB Lymphadenitis

	NTM	TB
Age:	1 – 5	any
Residence:	rural	urban
TB risk factors:	no	yes
CXR:	negative	10% positive
TST (mm)	0 – 15mm	>10 – 15mm

NEVER do incision & drainage

**Surgical excision diagnostic & curative for NTM
(if complete excision)**

7 year old male with a 2-month history of increasing lumbar pain and 5 day history of difficulty walking, vomiting, and progressive somnolence



Pott's Disease





Skeletal TB

- **Lymphohematogenous spread or direct extension from paravertebral node**
- **WBC normal**
- **Skeletal TB: young > old children (intense blood flow)**
 - **Adults: 6mos – 3 years after primary TB**
- **Vertebrae (~50%) > knee > hip**
- **S/sxs: “night cries”, restless sleep, gait changes, low-grade fever, gibbus deformity, reflex changes, clonus**







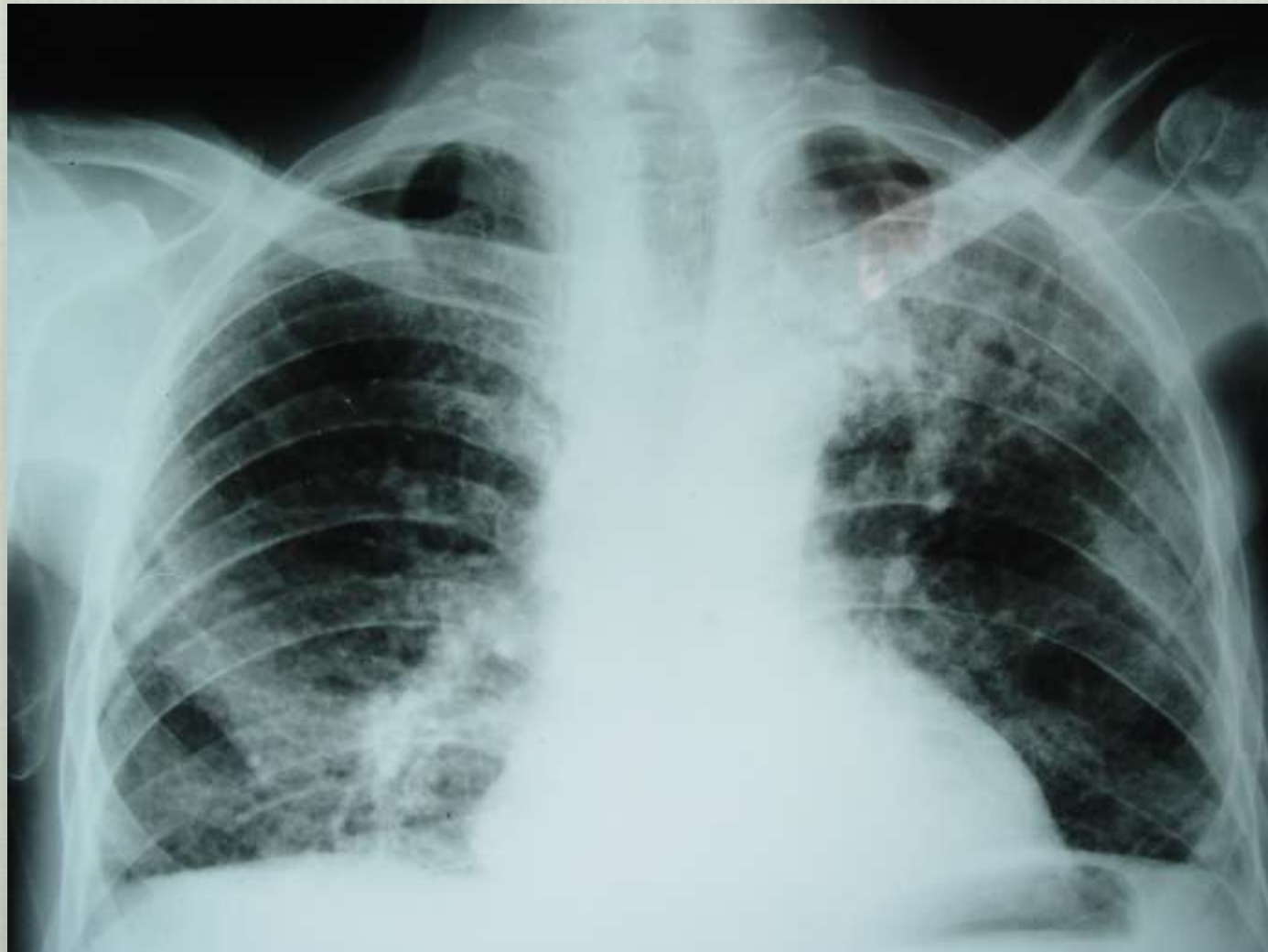
L3 - L5



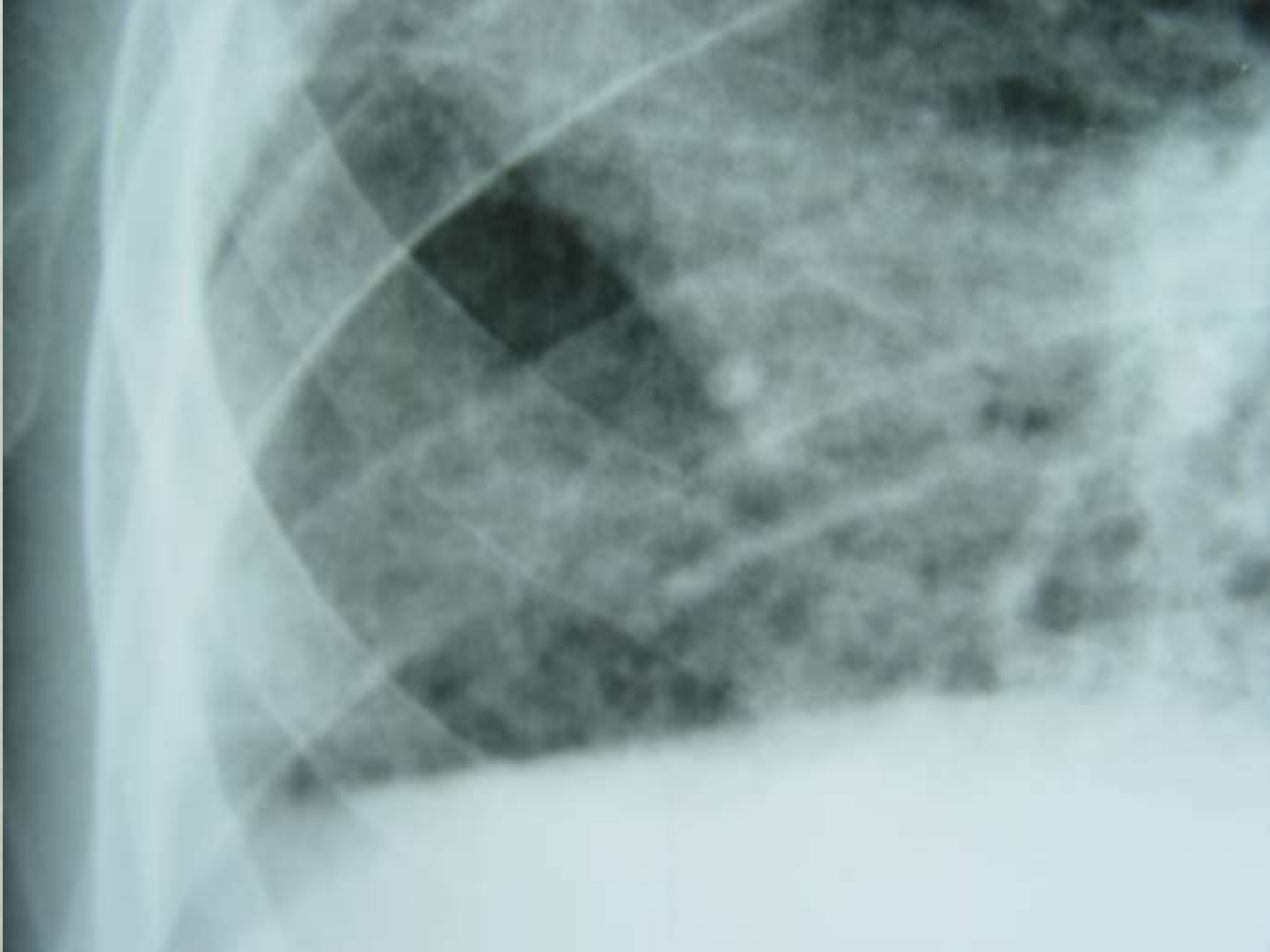
**76 yo presenting with abdominal TB
presenting as GI bleed. Miliary TB.**



76 yo - Miliary



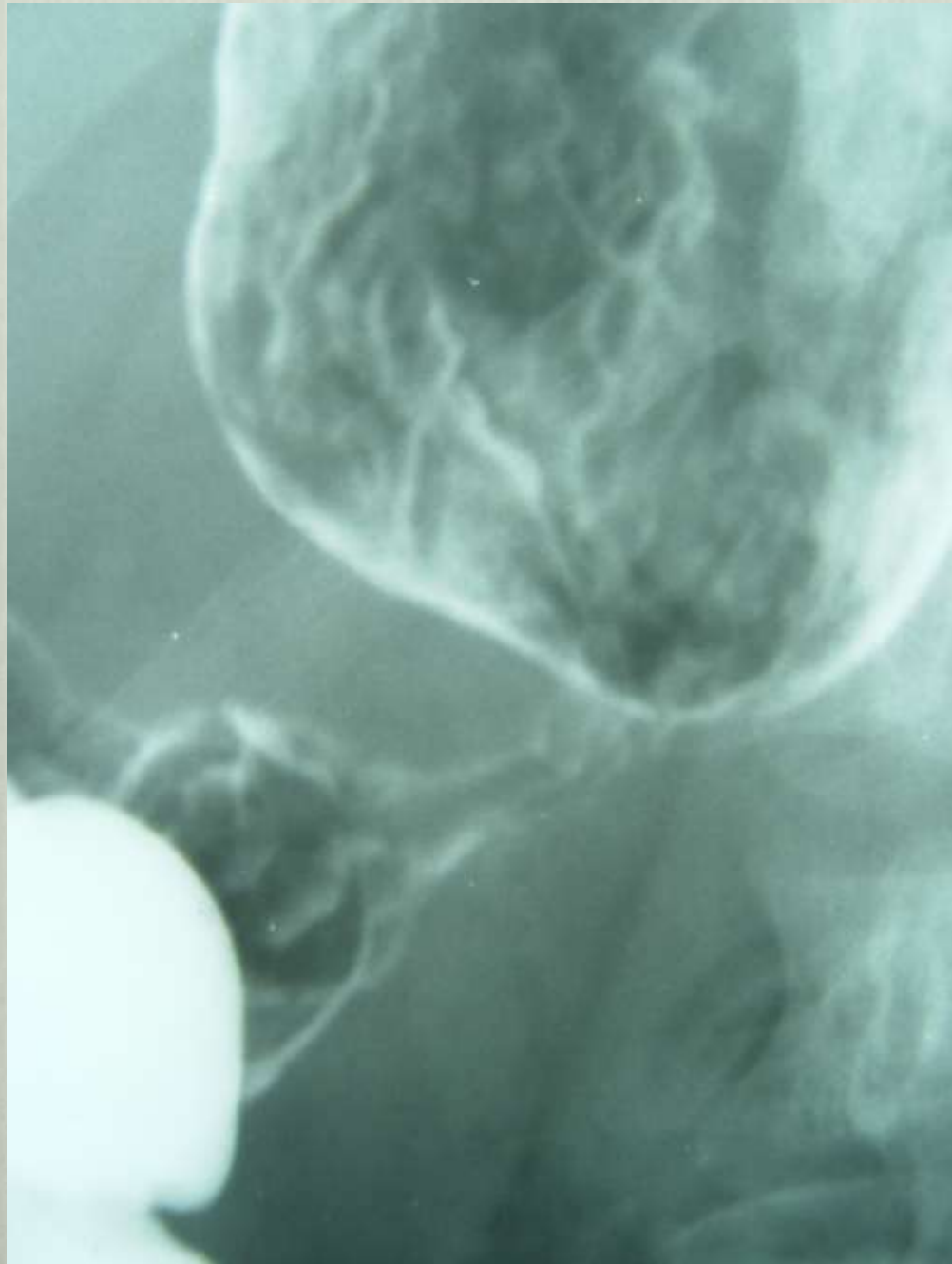
Miliary – 76 yo



44yo – 20 kg wt loss. HIV-negative















Erythema Induratum





Primary Cutaneous TB







**TB verrucosa
cutis**



Treatment of TB Disease in Children

- Pulmonary
 - INH, RIF x 6 mos + PZA for first 2 mos
 - Add ETH initially if risk of INH resistance
 - DOT
 - INH – resistant: RIF + PZA+ETH for 9 mos
 - MDR – depends on susceptibility; at least 18mos
- CNS, Disseminated
 - Usually start with 4 drugs
 - Usual length 9 – 12 months
 - Once daily initially, may use twice weekly later
- Steroids: meningitis, endobronchial, miliary with alveolar block, pericardial with constriction, vertebral with spinal root involvement

Practical Aspects of TB Management

- **Preganancy: INH, Rif, EMB. PZA avoided.**
- **DOT from beginning!**
- **1st line drugs administered together**
 - **Do not “split dosing” – lower efficacy**
- **GI upset common early in treatment (r/o hepatitis).
Administer with food rather than split dosing.**
- **Asymptomatic ALT increase (<3x normal) okay with INH/RIF**
- **Never add single drug to failing regimen.**
- **Pyridoxine (B6) supplementation to prevent INH-associated peripheral sensorimotor neuropathy**
 - **(small children, malnourished, pregnant, alcoholics, diabetes, renal dz)**

Scenarios:

- 2 month infant, mother has active pulmonary TB. Infant is breastfed... next steps?

Contagious vs noncontagious diseases?

- Hilar adenopathy only?
- Smear positive? Any treatment?
- Household members?

Infant: examine carefully

- TST/CXR at 3 mos & possibly 6 mos time
- ALWAYS start INH x 3 mos [window period]
- If TST, CXR, exam all normal at 3 mos, can stop INH
- Continues breastfeeding?

Mom has active disease, suspected contagious

- **Contact-household tracing**
- **Mother – infant separated until mother confirmed non-contagious (~2 weeks of tx, smear neg)**
- **Infant careful physical exam**
- **Started on INH (high risk of disseminated TB)**
- **TST/CXR 3 mos and possibly 6 mos**
- **INH stopped at 3 months of well**

Congenital TB



