Primary Care & Tuberculosis: Steps Toward TB Elimination

Vanderbilt Infectious Diseases Symposium

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Disclaimer

- I declare that within the past 12 months neither I, nor any immediate member of my family or our dog have had a financial relationship or any conflict of interest with any commercial interest that may have a direct bearing on the subject matter of this CME activity. Unfortunately.

Outline

1. Brief overview of TB epidemiology
2. Tuberculosis: what it is, and what it isn't
3. Diagnosis of "latent" TB Infection (TBI)
4. Treatment of TBI
5. Community partnerships to end TB

Tuberculosis – United States, 2018

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 68 / No. 11
March 22, 2019

World TB Day — March 24, 2019

World TB Day is observed each year on March 24. This observance provides an opportunity to raise awareness about tuberculosis (TB) and the measures needed to find, treat, and prevent this devastating disease.

In 2018, a provisional total of 9,029 TB cases were reported in the United States (incidence = 2.8 cases per 100,000 persons) (*1*), a decline from the 9,094 cases reported in 2017 and the lowest number of cases on record in the United States since reporting began in 1953. Increased diagnosis and treatment of latent TB infection remains essential to eliminating TB in the United States.

Worldwide, an estimated 10 million cases of TB were reported in 2017, a decline of 1.8% from

Tuberculosis — United States, 2018

Amish Talwar, MD[1,2]; Clarisse A. Tsang, MPH[1]; Sandy F. Price[1]; Robert H. Pratt[1]; William L. Walker, DVM, PhD[1]; Kristine M. Schmit, MD[1]; Adam J. Langer, DVM[1]

In 2018, a total of 9,029 new tuberculosis (TB) cases were reported in the United States, representing a 0.7% decrease from 2017.* The U.S. TB incidence in 2018 (2.8 per 100,000 persons) represented a 1.3% decrease from 2017; the rate among non–U.S.-born persons was >14 times that in U.S.-born persons. This report summarizes provisional TB surveillance data reported to CDC's National Tuberculosis Surveillance System (NTSS) through 2018. Although the total number of cases and incidence are the lowest ever reported in the United States, a recent model predicted that the U.S. TB elimination goal (annual incidence of <1 case per 1 million persons) will not be attained in the 21st century without greatly increased investment in detection and treatment of latent TB infection

https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6811a2-H.pdf

Tuberculosis – United States, 2018

Summary

What is already known about this topic?

The number of tuberculosis (TB) cases and incidence in the United States have steadily declined since 1993.

What is added by this report?

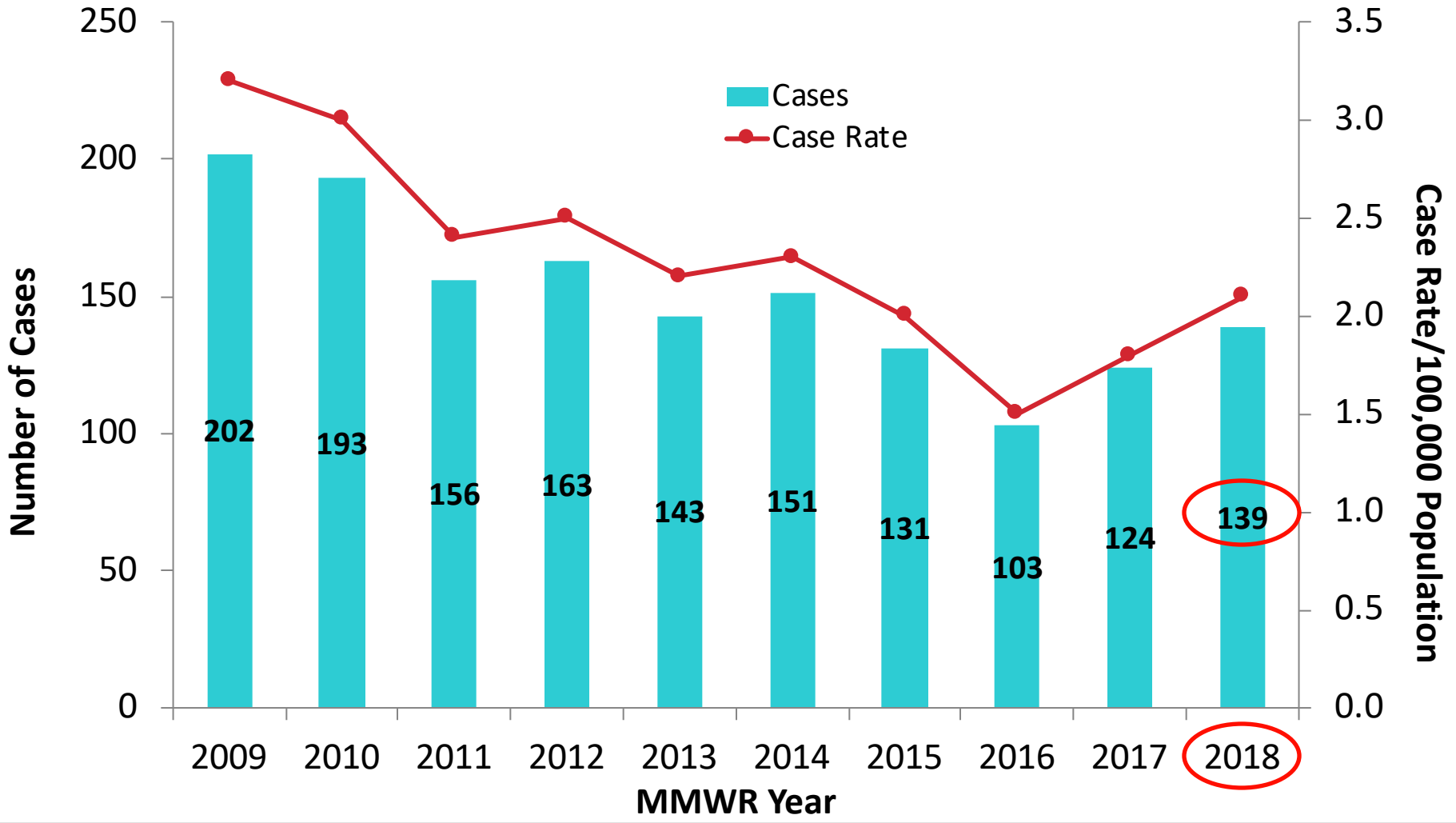
U.S. TB incidence in 2018 (2.8 cases per 100,000 persons) was the lowest ever reported. Non–U.S.-born persons accounted for approximately two thirds of cases.

What are the implications for public health practice?

The current decline in TB incidence is insufficient to eliminate TB in the United States in the 21st century. TB elimination will require enhanced surveillance, detection, and treatment. Focusing on populations that are at increased risk for latent TB infection will be important in achieving TB elimination.

Talwar A, Tsang CA, Price SF, et al. Tuberculosis — United States, 2018. MMWR Morb Mortal Wkly Rep 2019;68:257–262

Tennessee TB Cases and Rates, 2009-2018



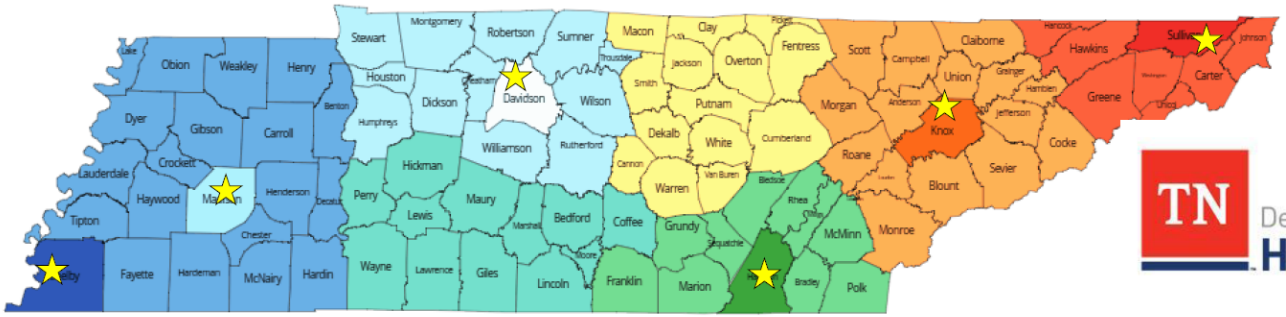
Source: National TB Indicators Project

Tennessee TB Surveillance – 2018

Tennessee Dept. of Health
TB Elimination Program

**Tennessee TB Cases and Rates*
by Region and County – 2018**

3/22/2019



Metro ☆	Cases	Rate
Memphis/Shelby	43	4.6
Jackson/Madison	1	1.0
Nashville/Davidson	29	4.1
Chatt./Hamilton	3	0.8
Knoxville/Knox	4	0.9
Sullivan	1	0.6

Rural Region	Cases	Rate
West TN	1	0.2
Mid-Cumberland	33	2.5
South Central	2	0.5
Upper Cumberland	8	2.3
Southeast TN	2	0.6
East TN	9	1.2
Northeast TN	3	0.8

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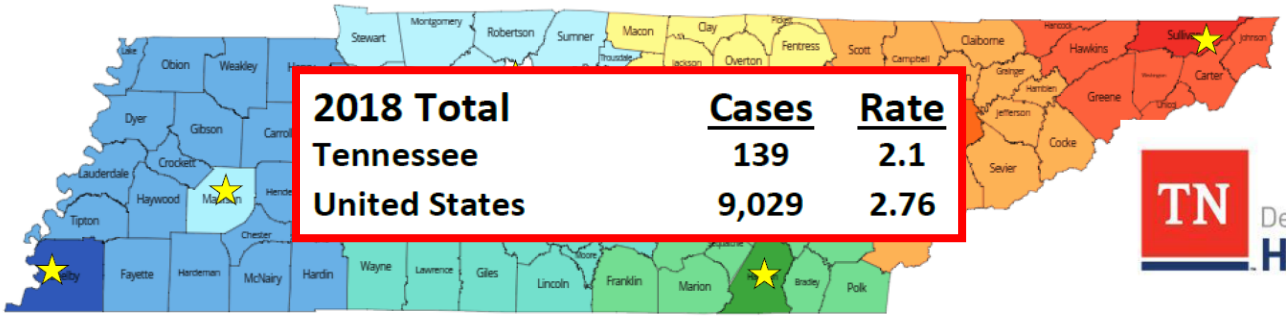

2018 Total	Cases	Rate
Tennessee	139	2.1
United States	9,029	2.76

TN Department of Health

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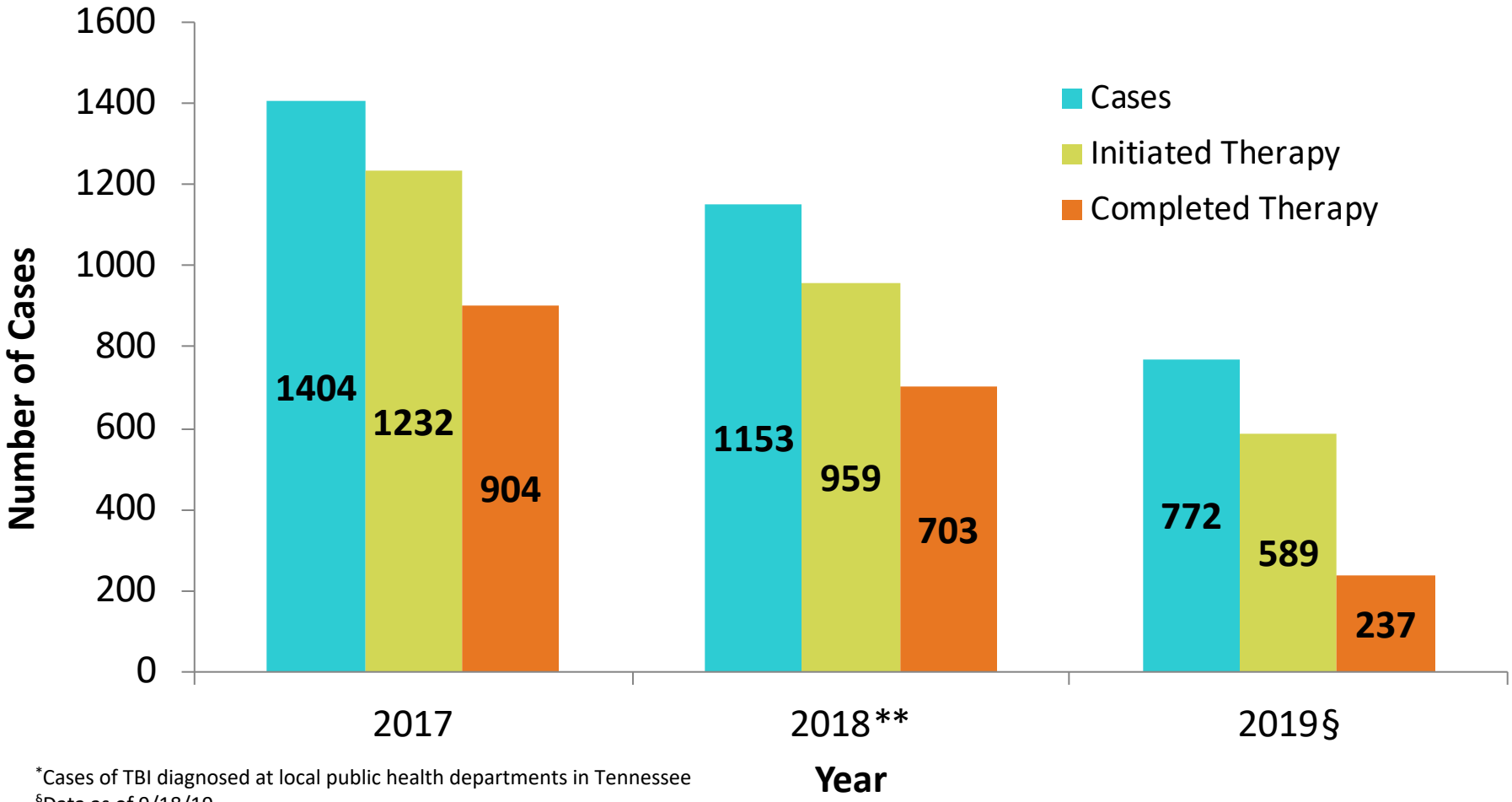
Tennessee TB Infection (TBI)*, 2017-2019§



*Cases of TBI diagnosed at local public health departments in Tennessee
§Data as of 9/18/19

Tuberculosis: what it *is*, and what it *isn't*

- **TB *is* …**
  - ✓ A disease affecting humans for 1000's of years
  - ✓ Caused by the bacterium *M. tuberculosis*
  - ✓ Infectious
  - ✓ Transmitted by aerosol
  - ✓ Can affect any organ system
  - ✓ Treatable, yet…
  - ✓ Subject to drug resistance
  - ✓ A pandemic, still
  - ✓ May be lethal untreated
  - ✓ Preventable

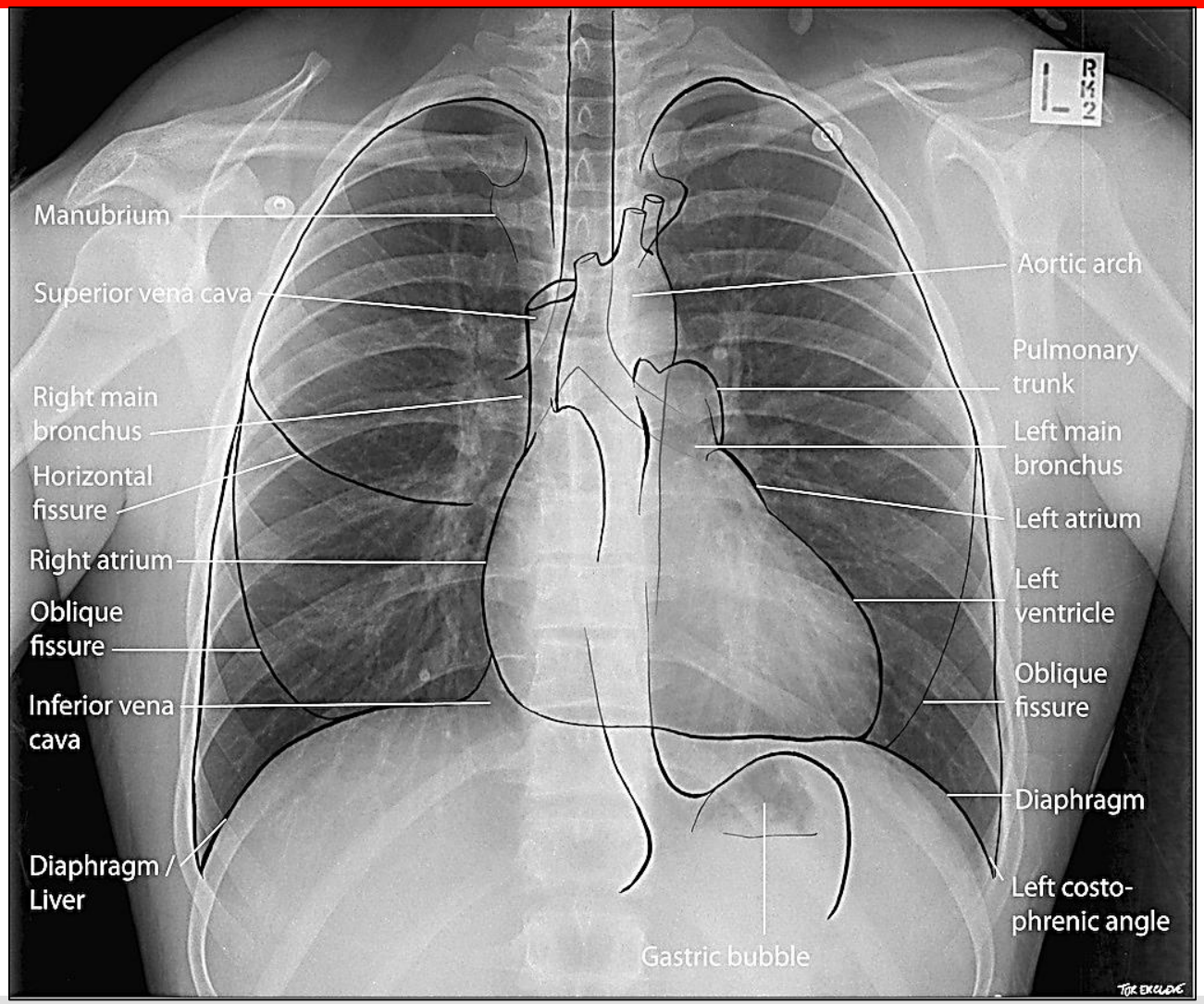
- **TB is *not* …**
  - ✓ An emerging infectious disease
  - ✓ Caused by a virus, prion, parasite or bad humors
  - ✓ Highly infectious
  - ✓ Transmitted by fomites
  - ✓ Limited disease focus
  - ✓ Untreatable, usually…
  - ✓ Always pansensitive
  - ✓ Geographically limited
  - ✓ Benign
  - ✓ Vaccine preventable*

Comparison of TB Disease vs "Latent" TB

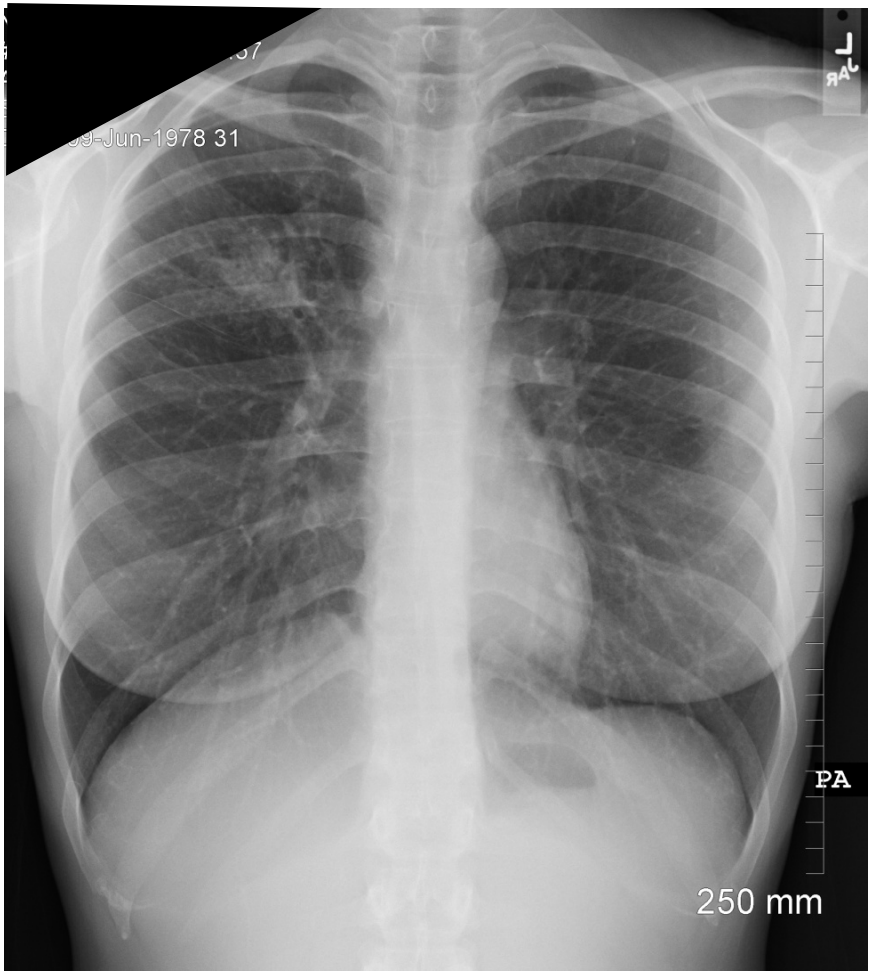
- **TB *disease***
  - ✓ Usually feels sick
  - ✓ Usually has symptoms
  - ✓ May transmit Mtb
  - ✓ Usually TST or IGRA+
  - ✓ May have abnormal CXR, AFB+/Cx+
  - ✓ Sometimes resolves without treatment
  - ✓ Significant morbidity
  - ✓ Needs treatment

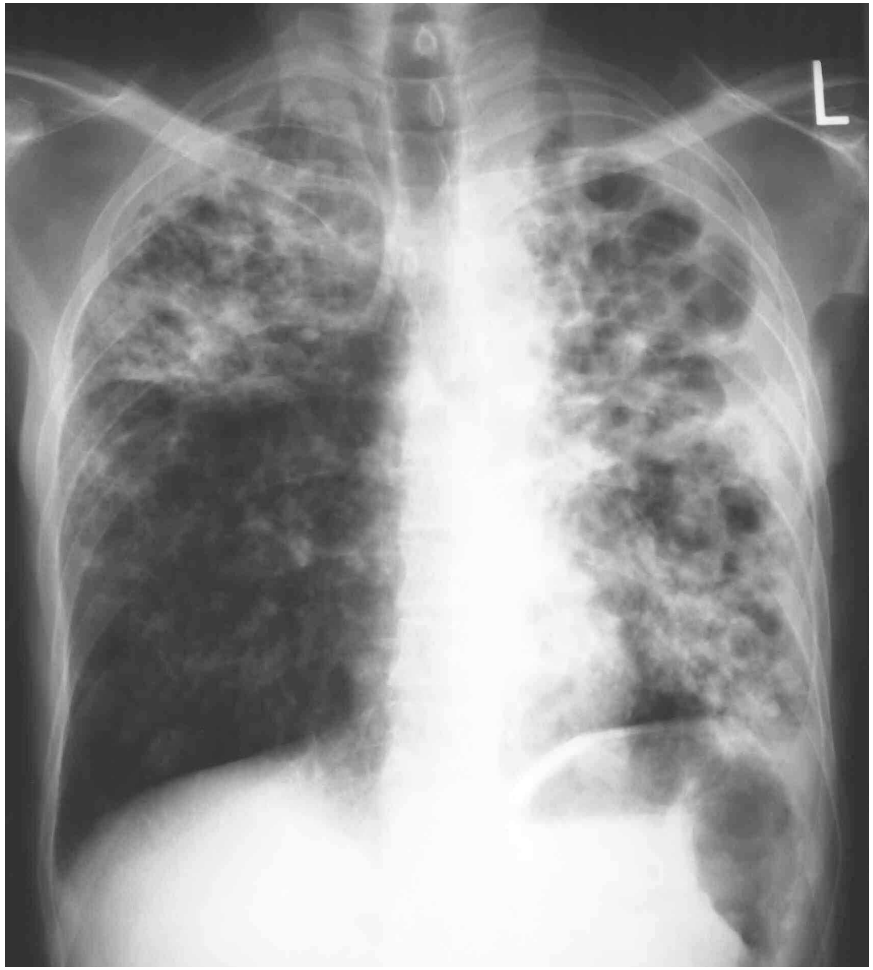
- **(Latent) TB *infection***
  - ✓ Does not feel sick
  - ✓ Asymptomatic
  - ✓ Cannot transmit Mtb
  - ✓ Usually TST or IGRA+
  - ✓ May have normal CXR, AFB-/Cx-
  - ✓ 5-10% risk of progression if immunocompetent
  - ✓ "Benign"
  - ✓ Needs treatment*

Normal Chest X-ray & Structures



Pop Quiz: Which is TB disease?





Diagnostic Process – TBI

1. **History and TB risk assessment**
   - Medical and social history
   - Risk for exposure to infectious TB disease
   - Risk for progression to TB disease if infected
2. **Test for TB infection**
   - Test to *treat* or test to *think?*
   - Choice of test – TST vs IGRA?
   - Interpretation of test results
3. **Chest X-ray (PA / lateral)**
   - Normal
   - Abnormal but nothing to suggest active TB disease
4. **Focused clinical examination**

Diagnosis of (L)TBI

TTBEP Criteria for Diagnosis of TBI:

1. No symptoms consistent with active TB disease
2. A positive TST or IGRA
3. A radiograph with no evidence of active TB disease
4. A focused clinical exam with no findings suggestive of extra-pulmonary or pulmonary TB disease
5. A negative sputum culture (if obtained)

A positive <u>test</u> is not a <u>diagnosis</u>

High-priority Candidates for Tx of (L)TBI

People who have a positive IGRA result or a TST reaction of 5 or more millimeters	People who have a positive IGRA result or a TST reaction of 10 or more millimeters
• HIV-infected persons** • Recent contacts of persons with infectious TB disease** • Persons with fibrotic changes on chest radiograph consistent with prior TB disease • Organ transplant recipients • Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for one month or longer, taking TNF-α antagonists, etc.)	• Recent arrivals to the U.S. (<5 years) from high-prevalence countries • Injection drug users • Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, or other health care facilities), etc. • Mycobacteriology laboratory personnel • Persons with medical conditions that increase the risk for progression to TB disease • Children <5 years of age; or children and adolescents exposed to adults in high-risk categories

**In certain circumstances, people in these categories may be given TBI treatment even if they do not have a positive TST or IGRA result.

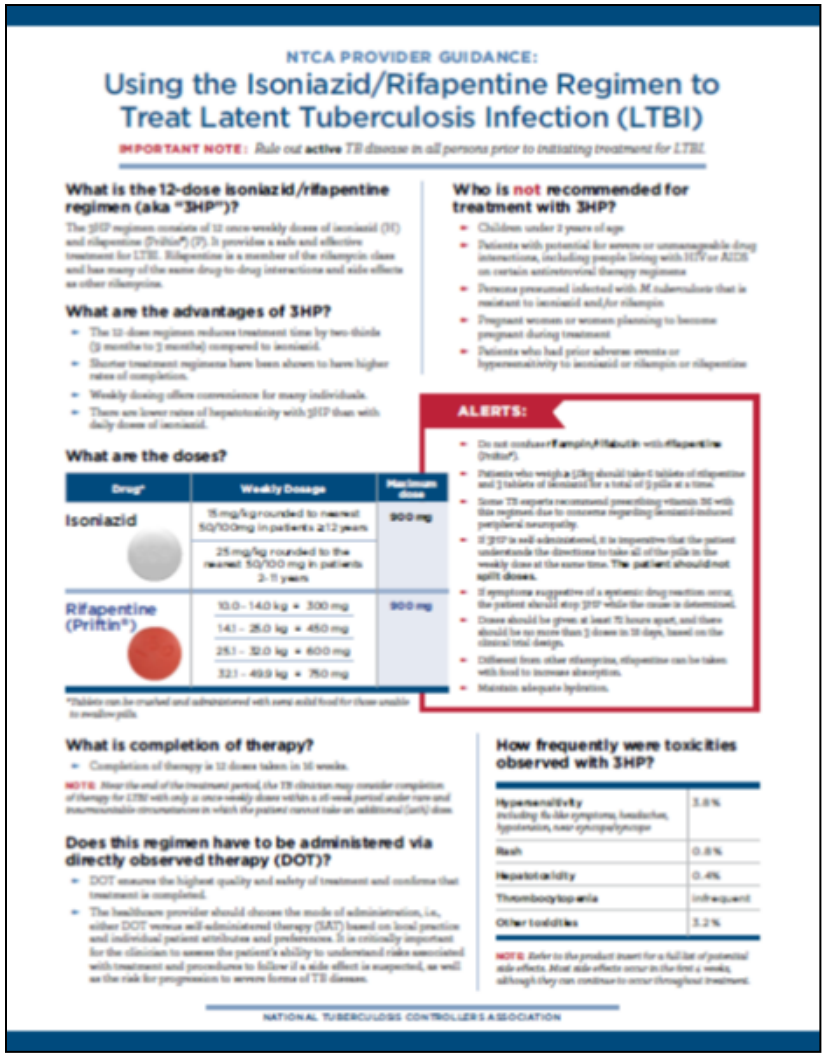
Treatment of TBI

1. Patient education about TB
   - ✓ What it is and what it isn't
   - ✓ Individual risk for progression
   - ✓ Risk vs benefit of treatment
2. Considerations in regimen selection
   - Drug susceptibility results of the presumed source case (if known)
   - Co-existing medical conditions
   - Potential for drug-drug interactions or toxicity
   - Priority for completion of TBI treatment
   - Logistical feasibility
   - Patient preference

Current Regimens for Treatment of TBI

Regimen	Drug/ Duration	Interval	Minimum Doses	Comments
"3HP"	**Isoniazid - Rifapentine X 12 weeks**	**Once weekly**	**12 within 16 weeks**	• Regimen generally preferred by TTBEP to ensure treatment completion for patients ≥ 2 years of age • Caveats!
"4R"	**Rifampin X 4 months**	**Daily**	**120 within 6 months**	• Used for adults and children ≥2 years of age who cannot tolerate the "3HP" regimen or have been exposed to INH-resistant TB • Regimen preferred by TTBEP for children <2 years of age
"9H"	**Isoniazid X 9 months**	**Daily**	**270 within 12 months**	• Recommended regimen for people with HIV*, for children, and for people with chest radiograph findings suggestive of previous TB
		Twice weekly	**76 within 12 months**	• DOPT **must** be used

NTCA Provider Guidance on Use of "3HP"



NTCA PROVIDER GUIDANCE:

Using the Isoniazid/Rifapentine Regimen to Treat Latent Tuberculosis Infection (LTBI)

IMPORTANT NOTE: *Rule out* **active** *TB disease in all persons prior to initiating treatment for LTBI.*

What is the 12-dose isoniazid/rifapentine regimen (aka "3HP")?

The 3HP regimen consists of 12 once-weekly doses of isoniazid (H) and rifapentine (Priftin®) (P). It provides a safe and effective treatment for LTBI. Rifapentine is a member of the rifamycin class and has many of the same drug-to-drug interactions and side effects as other rifamycins.

What are the advantages of 3HP?

- The 12-dose regimen reduces treatment time by two-thirds (3 months to 3 months) compared to isoniazid.
- Shorter treatment regimens have been shown to have higher rates of completion.
- Weekly dosing offers convenience for many individuals.
- There are lower rates of hepatotoxicity with 3HP than with daily dosing of isoniazid.

What are the doses?

Drug*	Weekly Dosage	Maximum dose
Isoniazid	15 mg/kg rounded to nearest 50/100 mg in patients ≥12 years	900 mg
	25 mg/kg rounded to the nearest 50/100 mg in patients 2–11 years	
Rifapentine (Priftin®)	10.0 – 14.0 kg = 300 mg	900 mg
	14.1 – 25.0 kg = 450 mg	
	25.1 – 32.0 kg = 600 mg	
	32.1 – 49.9 kg = 750 mg	

*Tablets can be crushed and administered with some solid food for those unable to swallow pills.

Who is not recommended for treatment with 3HP?

- Children under 2 years of age
- Patients with potential for severe or unmanageable drug interactions, including people living with HIV or AIDS on certain antiretroviral therapy regimens
- Persons presumed infected with *M. tuberculosis* that is resistant to isoniazid and/or rifampin
- Pregnant women or women planning to become pregnant during treatment
- Patients who had prior adverse events or hypersensitivity to isoniazid or rifampin or rifapentine

ALERTS:

- Do not coadminister rifampin/rifabutin with rifapentine (Priftin®).
- Patients who weigh a 25kg should take 5 tablets of rifapentine and 5 tablets of isoniazid for a total of 5 pills at a time.
- Some TB experts recommend prescribing vitamin B6 with this regimen due to concerns regarding isoniazid-induced peripheral neuropathy.
- If 3HP is self-administered, it is imperative that the patient understands the directions to take all of the pills in the weekly dose at the same time. **The patient should not split doses.**
- If symptoms suggestive of a systemic drug reaction occur, the patient should stop 3HP while the cause is determined.
- Doses should be given at least 72 hours apart, and there should be no more than 3 doses in 10 days, based on the clinical trial design.
- Different from other rifamycins, rifapentine can be taken with food to increase absorption.
- Maintain adequate hydration.

What is completion of therapy?

- Completion of therapy is 12 doses taken in 16 weeks.

NOTE: *Near the end of the treatment period, the TB clinician may consider completion of therapy for LTBI with only a once-weekly dose within a 28-week period under rare and insurmountable circumstances in which the patient cannot take an additional (last) dose.*

Does this regimen have to be administered via directly observed therapy (DOT)?

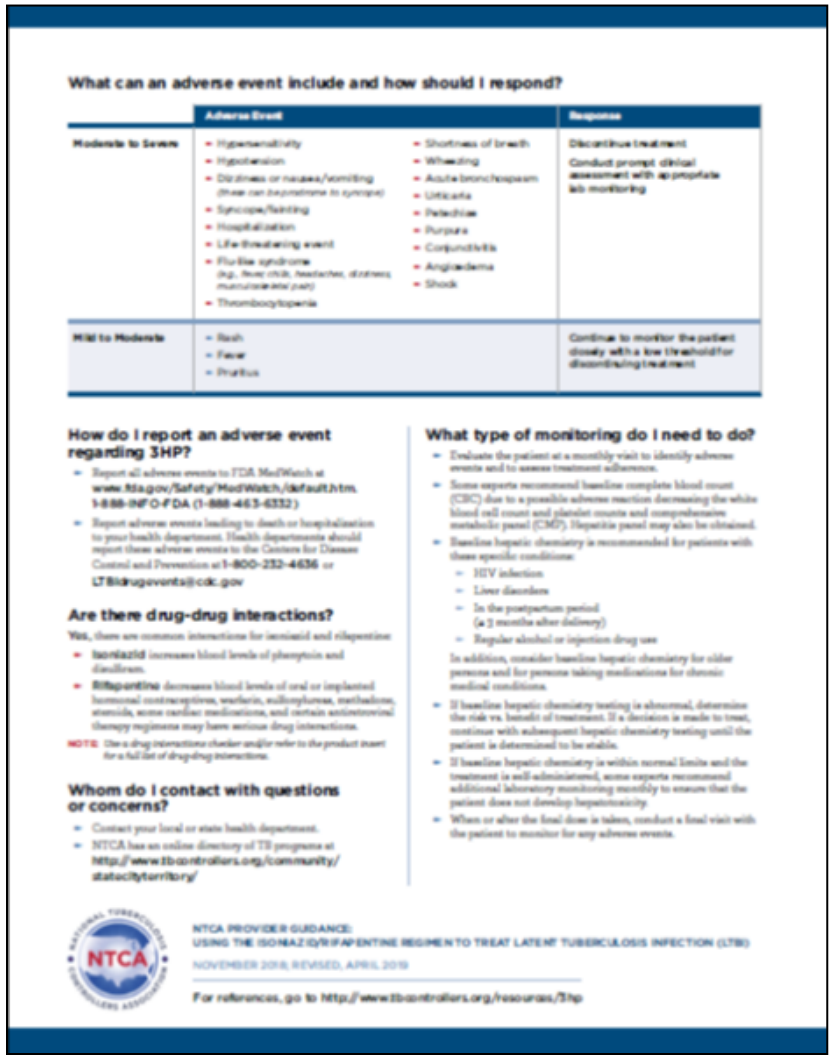
- DOT ensures the highest quality and safety of treatment and confirms that treatment is completed.
- The healthcare provider should choose the mode of administration, i.e., either DOT versus self-administered therapy (SAT) based on local practice and individual patient attributes and preferences. It is critically important for the clinician to assess the patient's ability to understand risks associated with treatment and procedures to follow if a side effect is suspected, as well as the risk for progression to severe forms of TB disease.

How frequently were toxicities observed with 3HP?

Hypersensitivity including flu-like symptoms, headaches, hypotension, near-syncope/syncope	3.8%
Rash	0.8%
Hepatotoxicity	0.4%
Thrombocytopenia	Infrequent
Other toxicities	3.2%

NOTE: *Refer to the product insert for a full list of potential side effects. Most side effects occur in the first 4 weeks, although they can continue to occur throughout treatment.*

NATIONAL TUBERCULOSIS CONTROLLERS ASSOCIATION



What can an adverse event include and how should I respond?

	Adverse Event		Response
Moderate to Severe	• Hypersensitivity • Hypotension • Dizziness or nausea/vomiting (these can be/sometimes to syncope) • Syncope/fainting • Hospitalization • Life-threatening event • Flu-like syndrome (e.g., fever, chills, headaches, dizziness, myalgia/arthralgia/pain) • Thrombocytopenia	• Shortness of breath • Wheezing • Acute bronchospasm • Urticaria • Petechiae • Purpura • Conjunctivitis • Angioedema • Shock	Discontinue treatment Conduct prompt clinical assessment with appropriate lab monitoring
Mild to Moderate	• Rash • Fever • Pruritus		Continue to monitor the patient closely with a low threshold for discontinuing treatment

How do I report an adverse event regarding 3HP?

- Report all adverse events to FDA MedWatch at www.fda.gov/Safety/MedWatch/default.htm, 1-888-INFO-FDA (1-888-463-6332)
- Report adverse events leading to death or hospitalization to your health department. Health departments should report these adverse events to the Centers for Disease Control and Prevention at 1-800-232-4636 or LTBIdrugevents@cdc.gov

Are there drug-drug interactions?

Yes, there are common interactions for isoniazid and rifapentine:

- **Isoniazid** increases blood levels of phenytoin and disulfiram.
- **Rifapentine** decreases blood levels of oral or implanted hormonal contraceptives, warfarin, sulfonylureas, methadone, steroids, some cardiac medications, and certain antiretroviral therapy regimens may have serious drug interactions.

NOTE: Use a drug interactions checker and/or refer to the product insert for a full list of drug-drug interactions.

Whom do I contact with questions or concerns?

- Contact your local or state health department.
- NTCA has an online directory of TB programs at http://www.tbcontrollers.org/community/statecityterritory/

What type of monitoring do I need to do?

- Evaluate the patient at a monthly visit to identify adverse events and to assess treatment adherence.
- Some experts recommend baseline complete blood count (CBC) due to a possible adverse reaction decreasing the white blood cell count and platelet counts and comprehensive metabolic panel (CMP). Hepatitis panel may also be obtained.
- Baseline hepatic chemistry is recommended for patients with these specific conditions:
  - HIV infection
  - Liver disorders
  - In the postpartum period (≥ 3 months after delivery)
  - Regular alcohol or injection drug use

  In addition, consider baseline hepatic chemistry for older persons and for persons taking medications for chronic medical conditions.
- If baseline hepatic chemistry testing is abnormal, determine the risk vs. benefit of treatment. If a decision is made to treat, continue with subsequent hepatic chemistry testing until the patient is determined to be stable.
- If baseline hepatic chemistry is within normal limits and the treatment is self-administered, some experts recommend additional laboratory monitoring monthly to ensure that the patient does not develop hepatotoxicity.
- When or after the final dose is taken, conduct a final visit with the patient to monitor for any adverse events.

NTCA

NTCA PROVIDER GUIDANCE:
USING THE ISONIAZID/RIFAPENTINE REGIMEN TO TREAT LATENT TUBERCULOSIS INFECTION (LTBI)

NOVEMBER 2018, REVISED, APRIL 2019

For references, go to http://www.tbcontrollers.org/resources/3hp

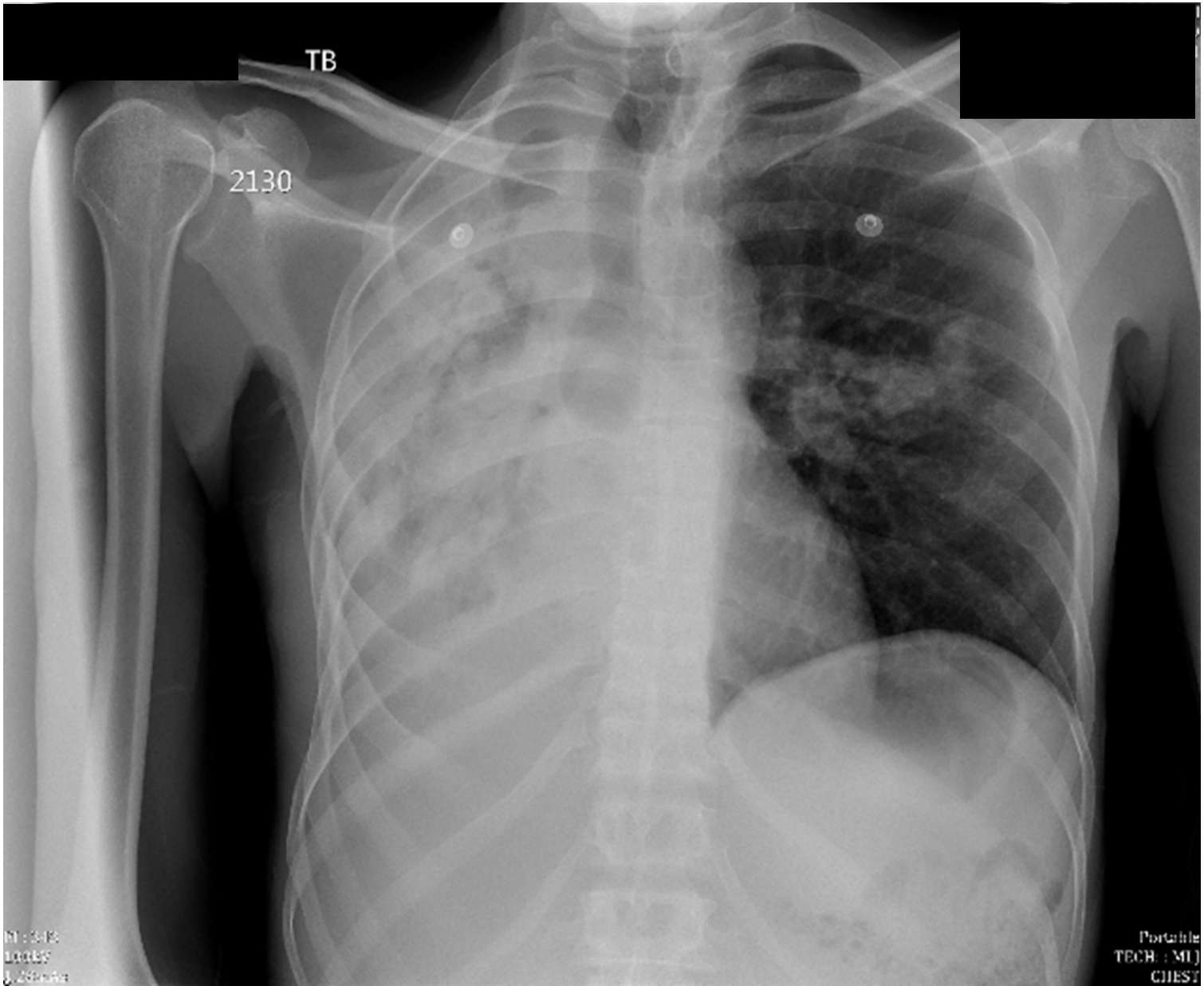
http://www.tbcontrollers.org/

TN Department of Health

OK, so *what?!*

This is what TB can do.

Portable CXR – 8/10/2019



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Chest CT
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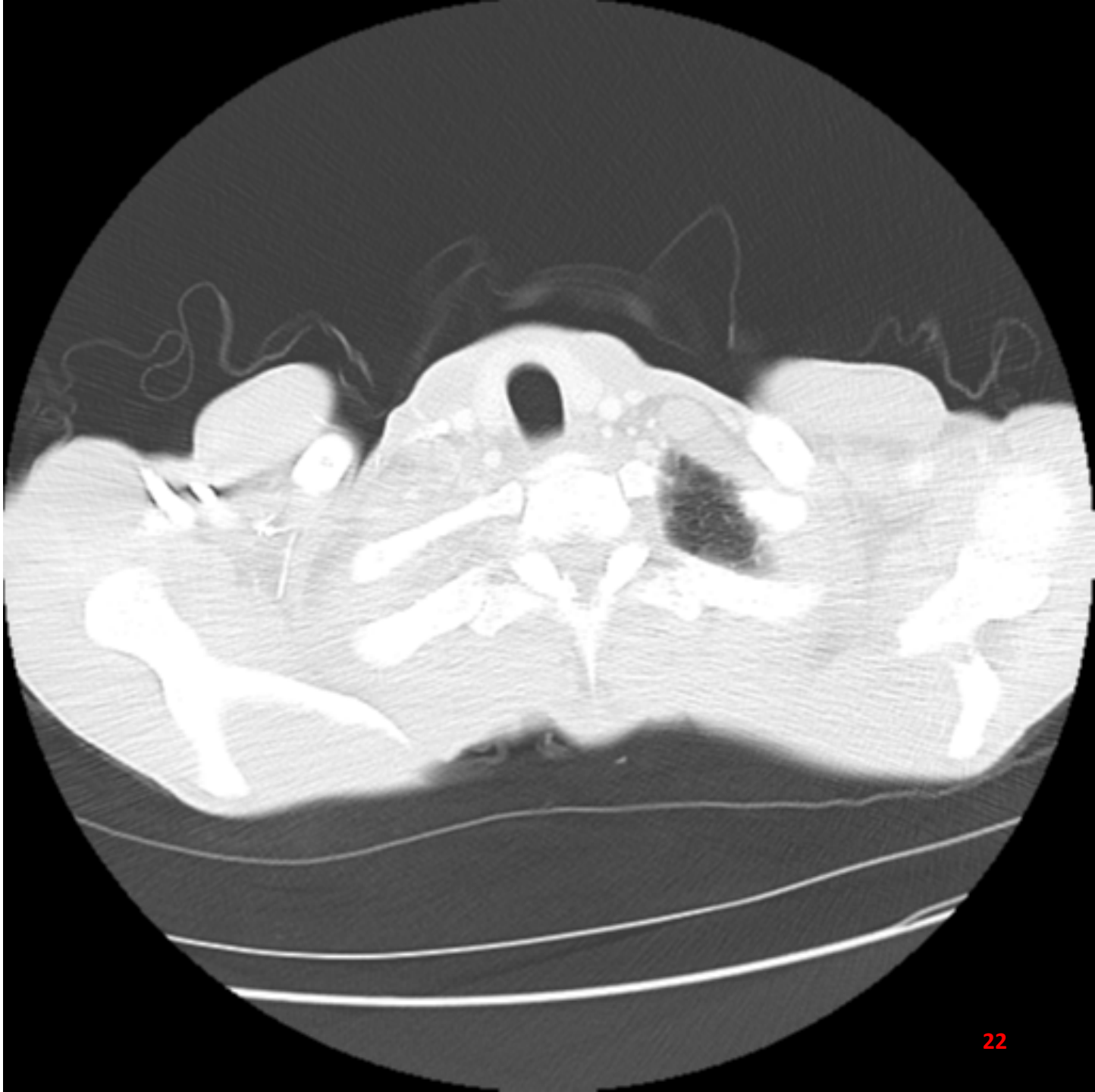

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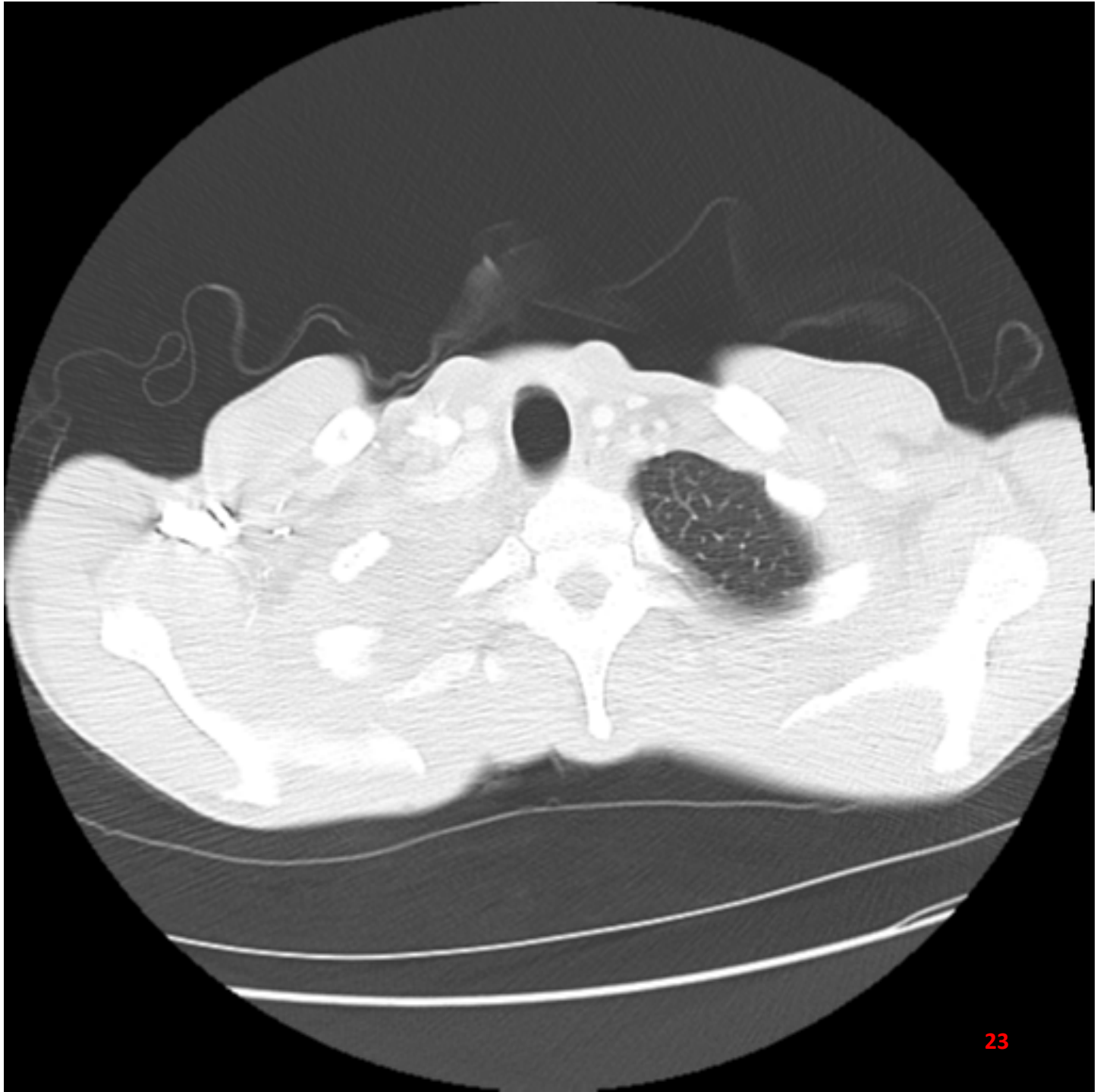

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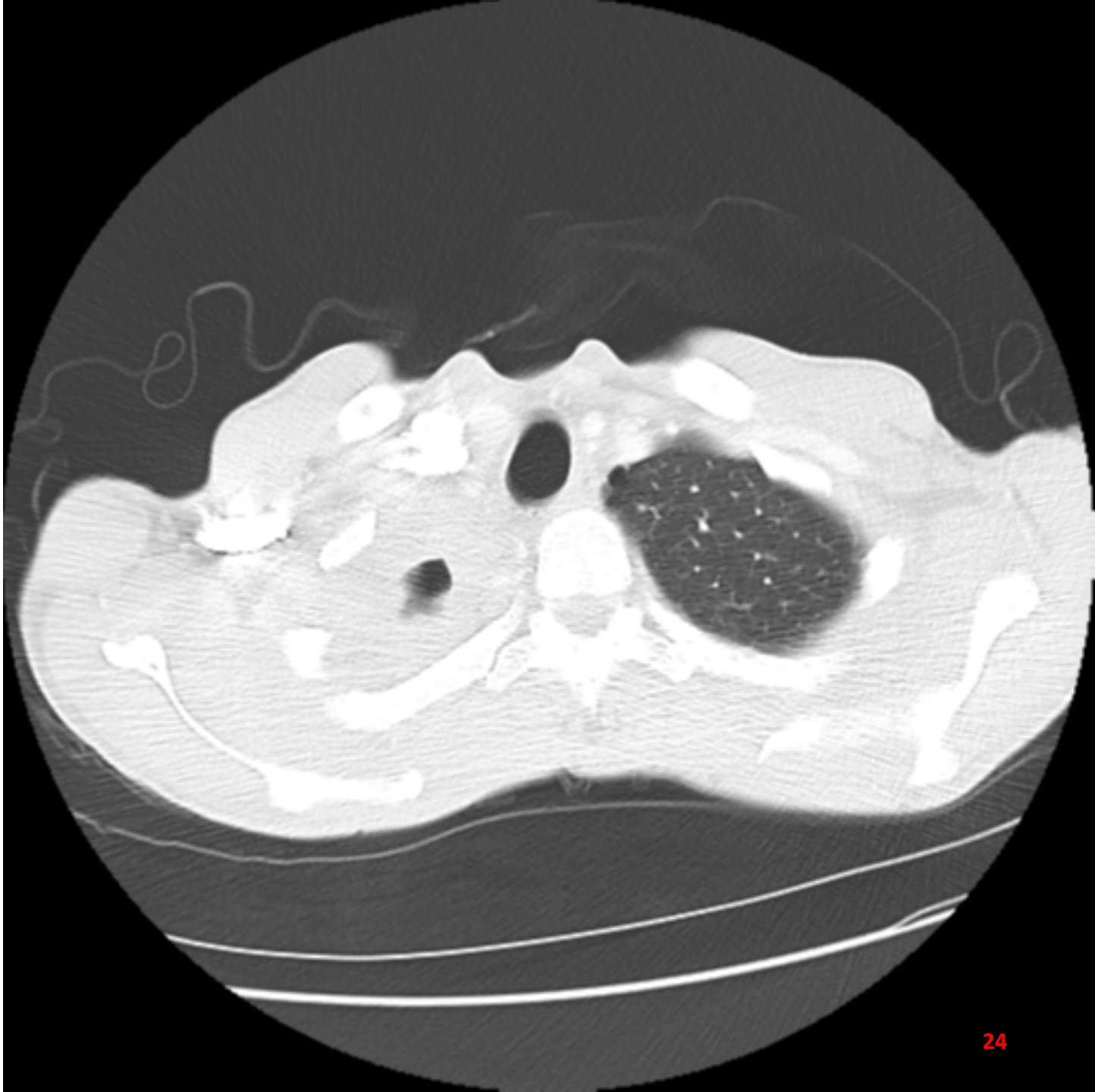

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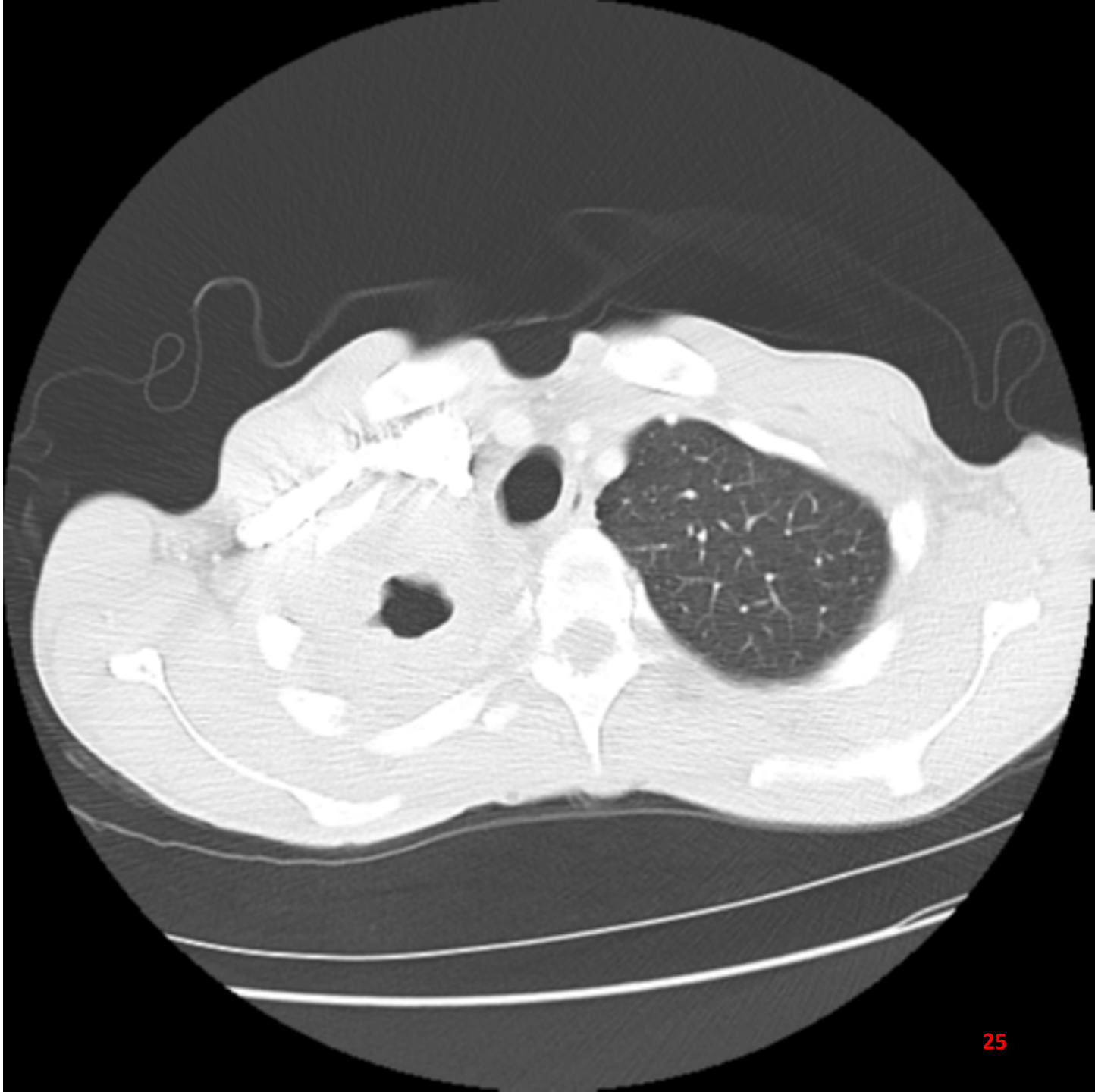

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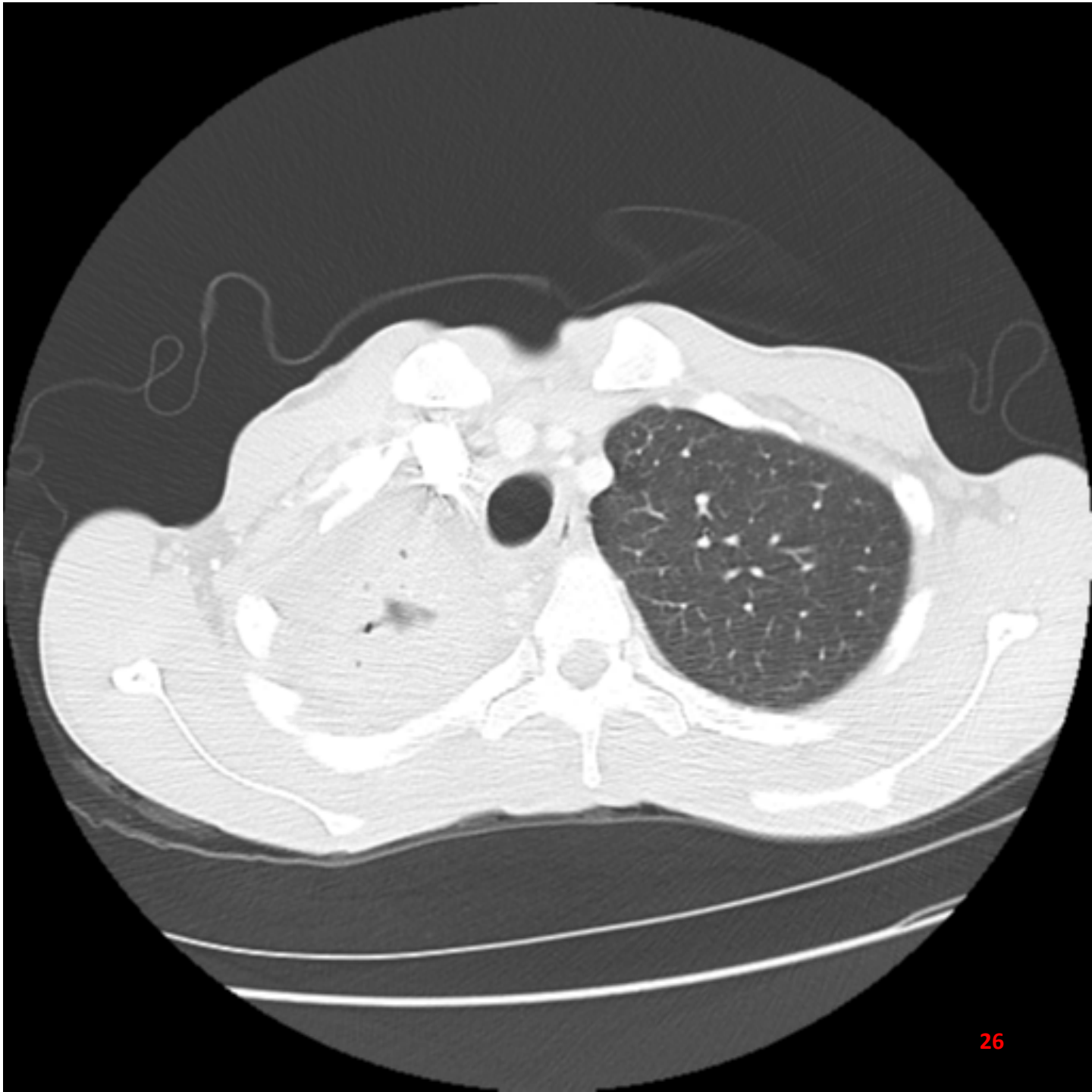

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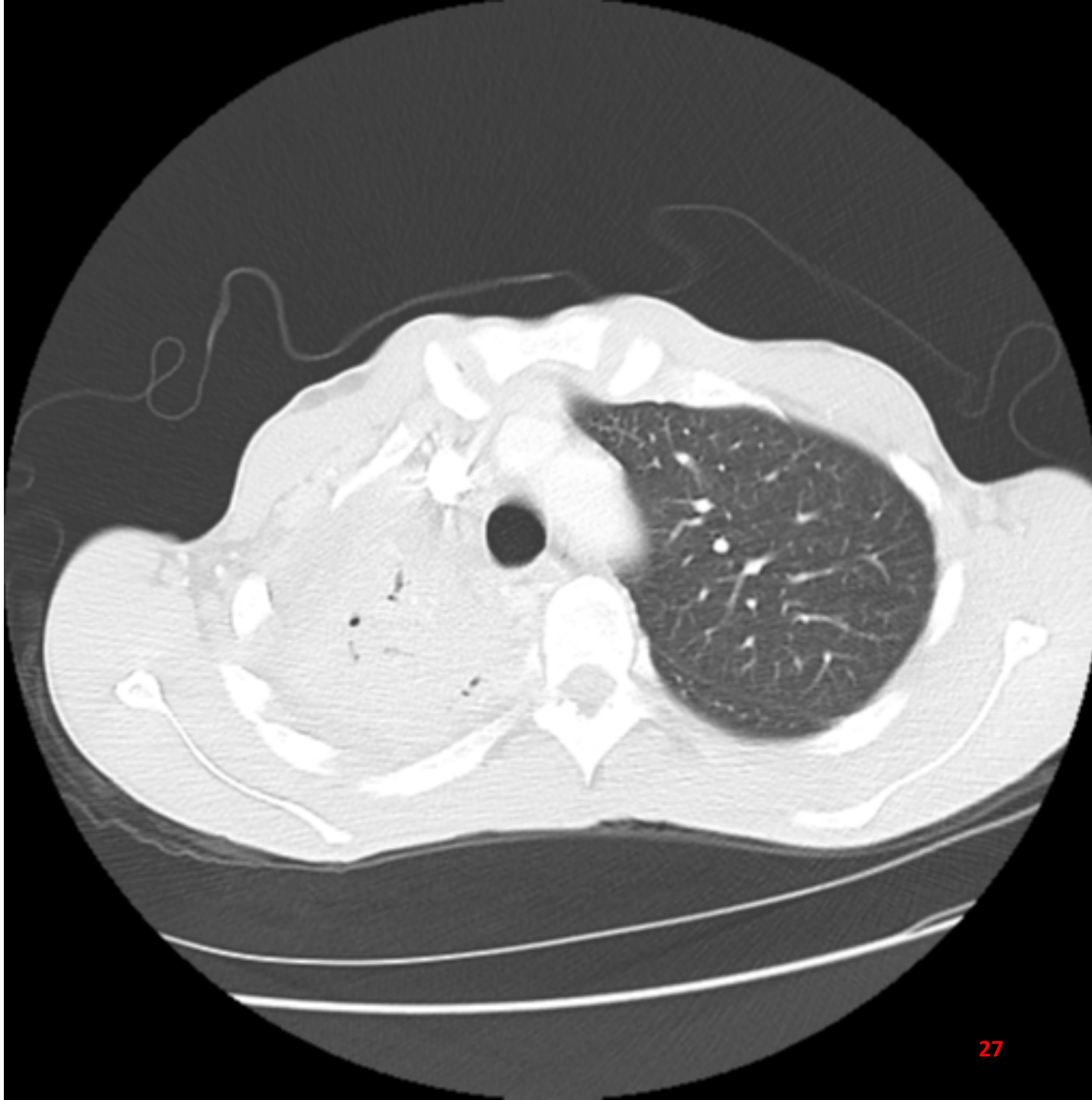

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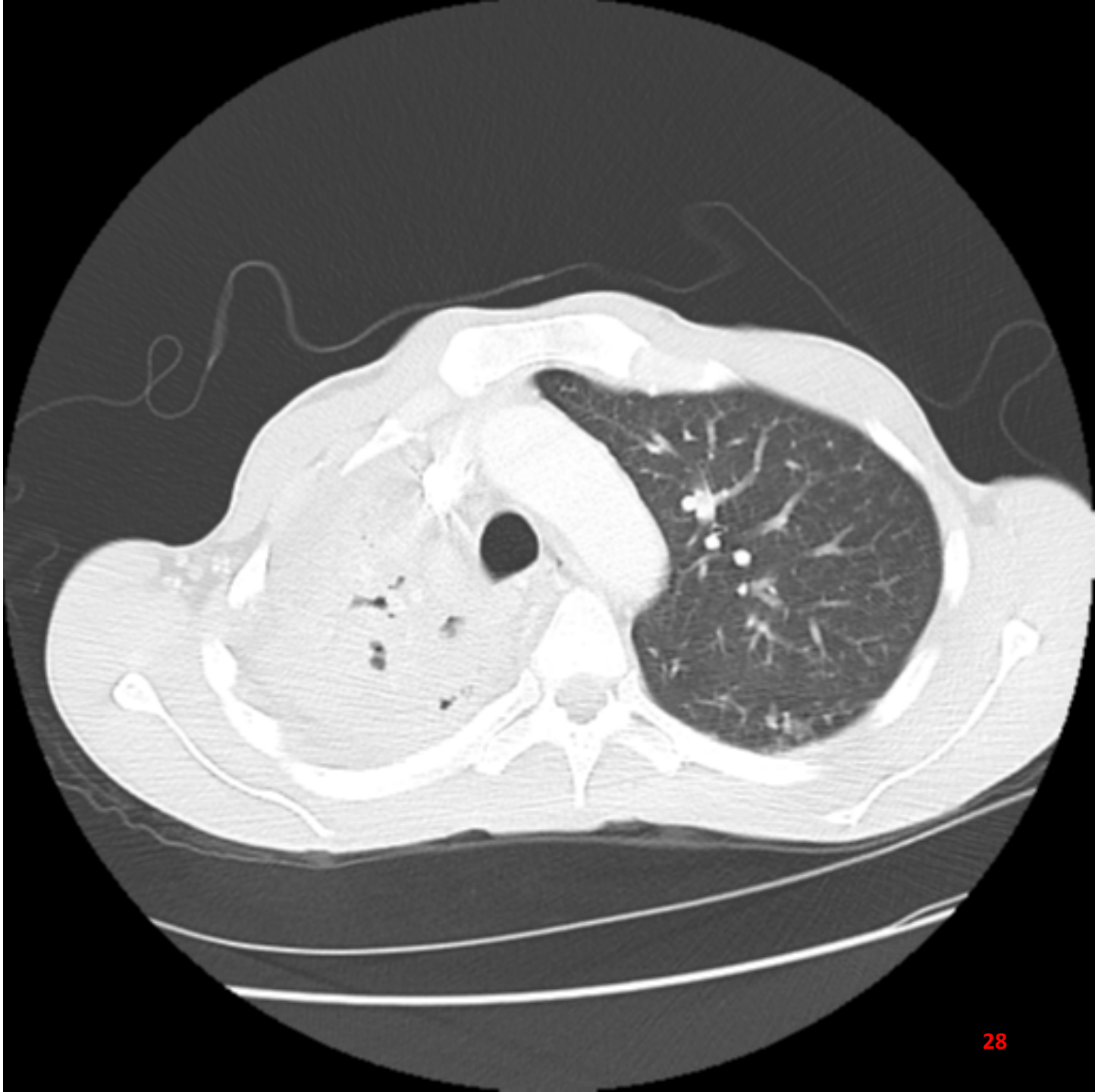

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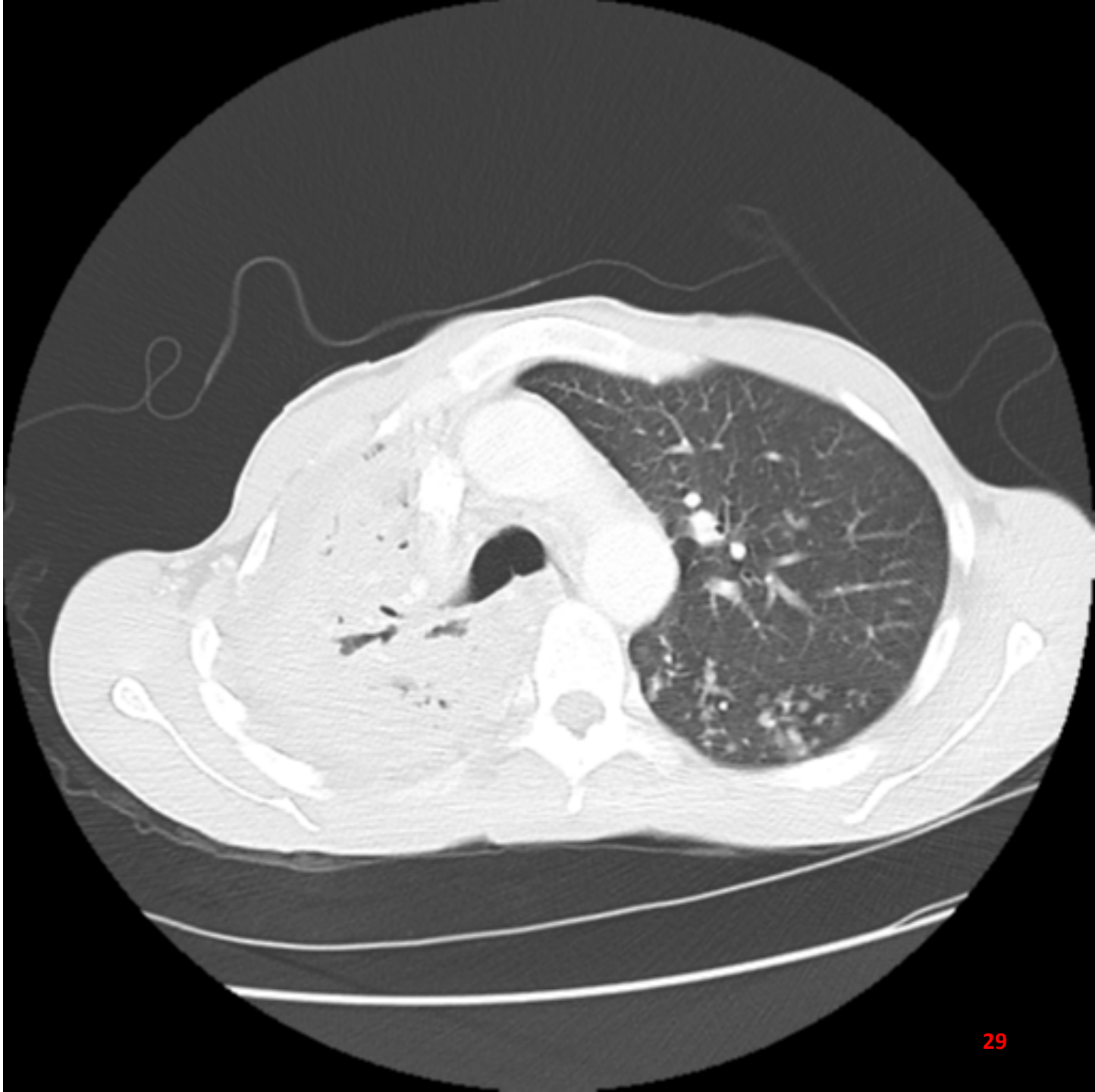

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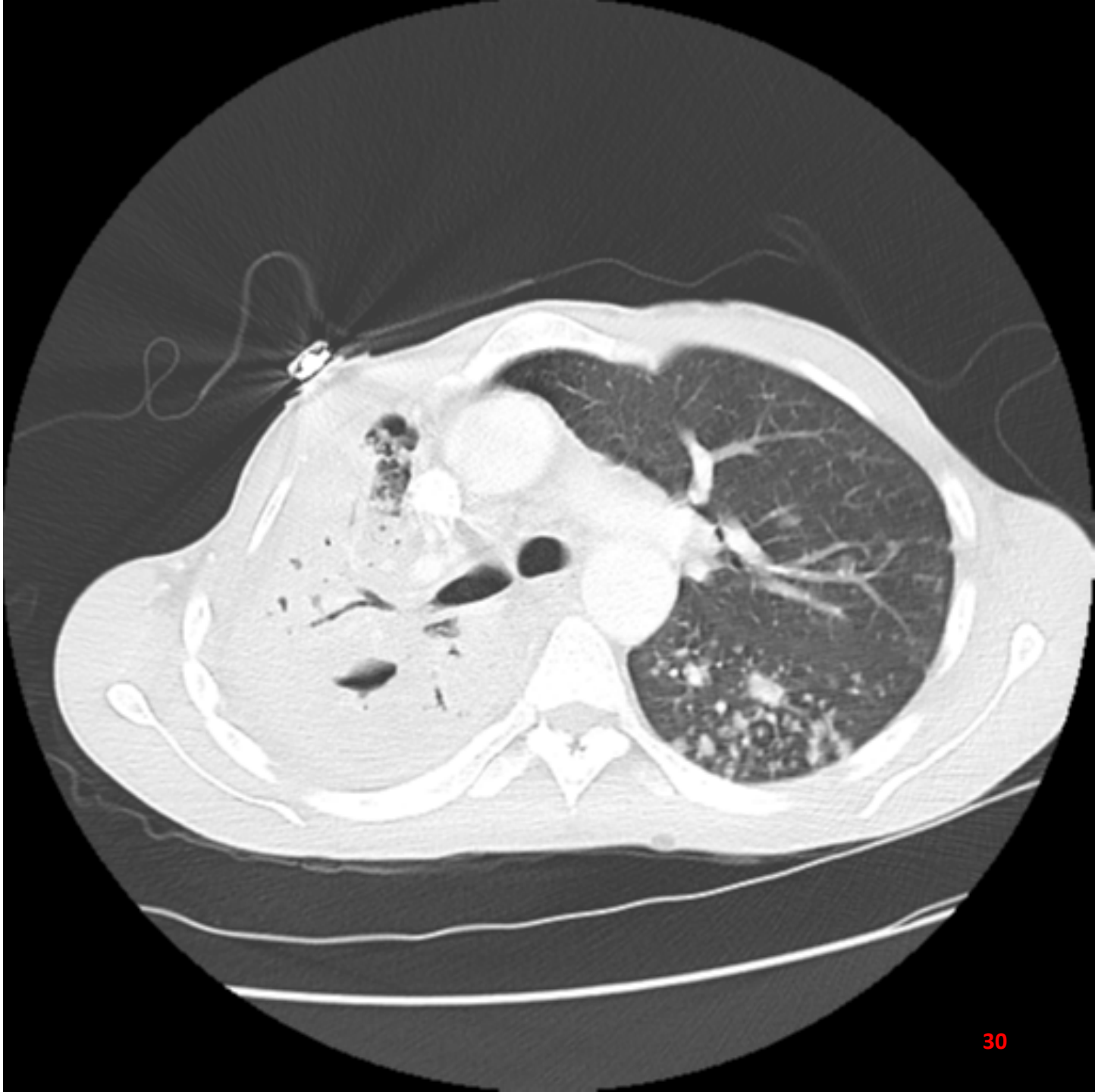

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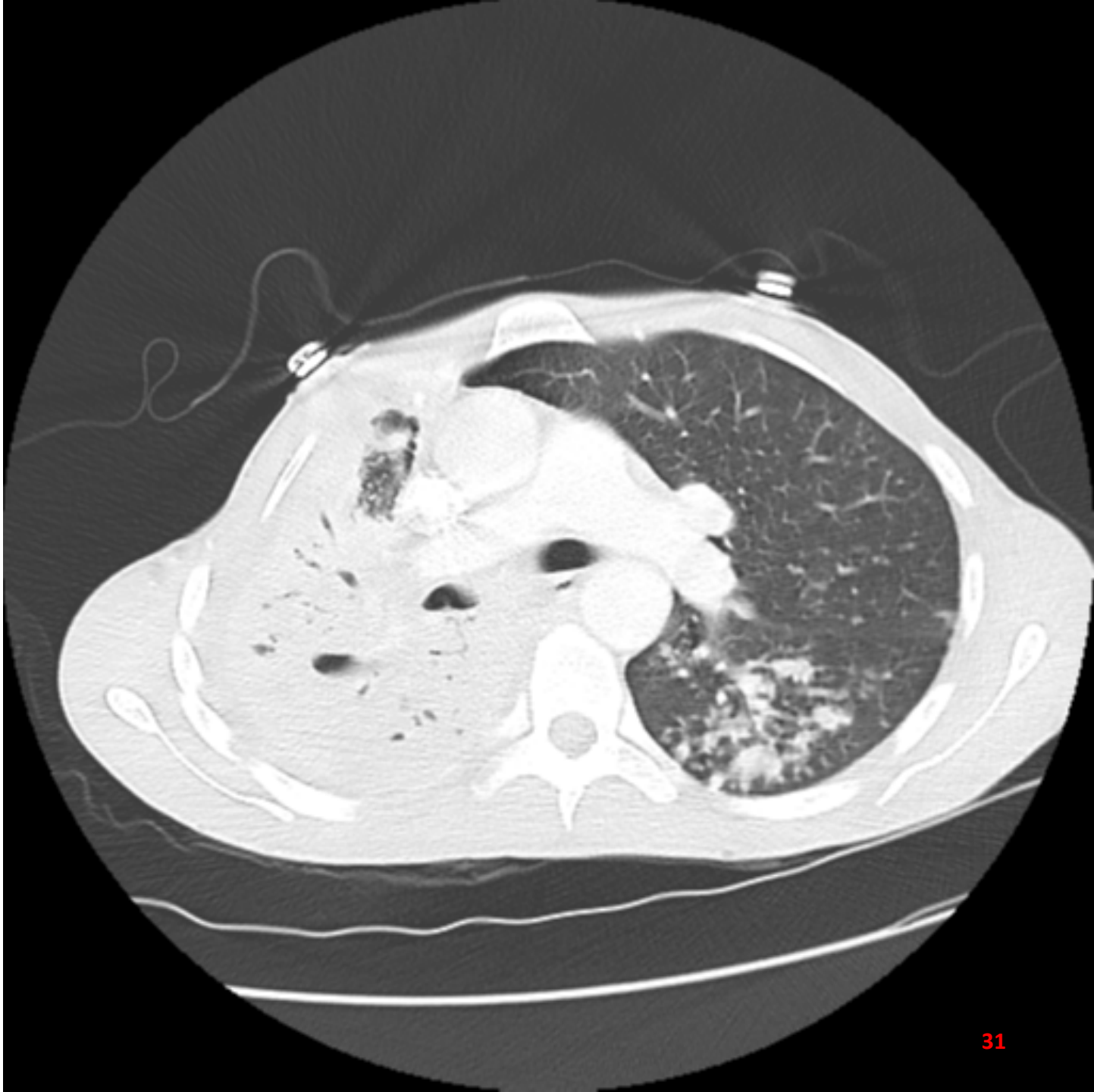

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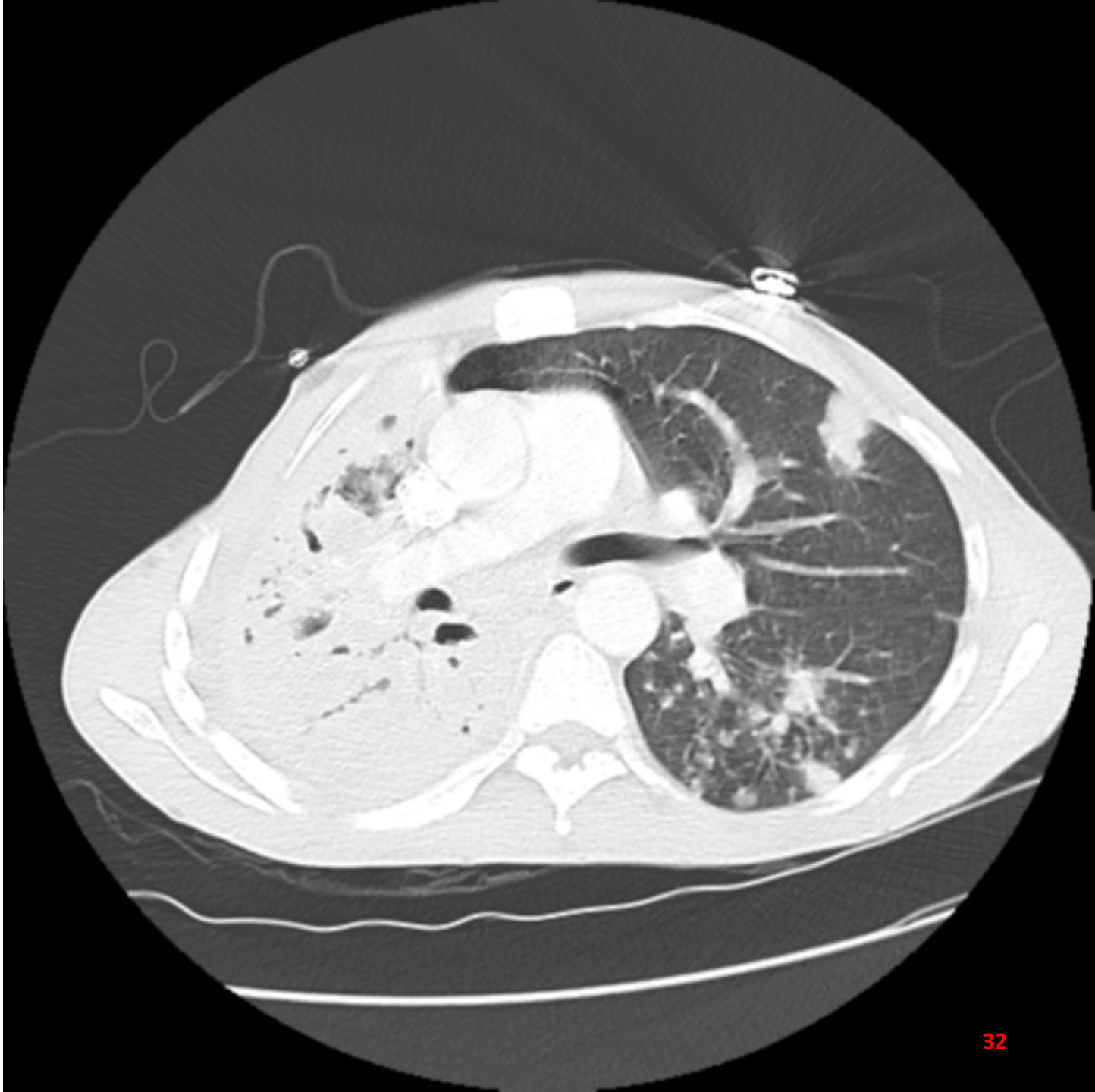

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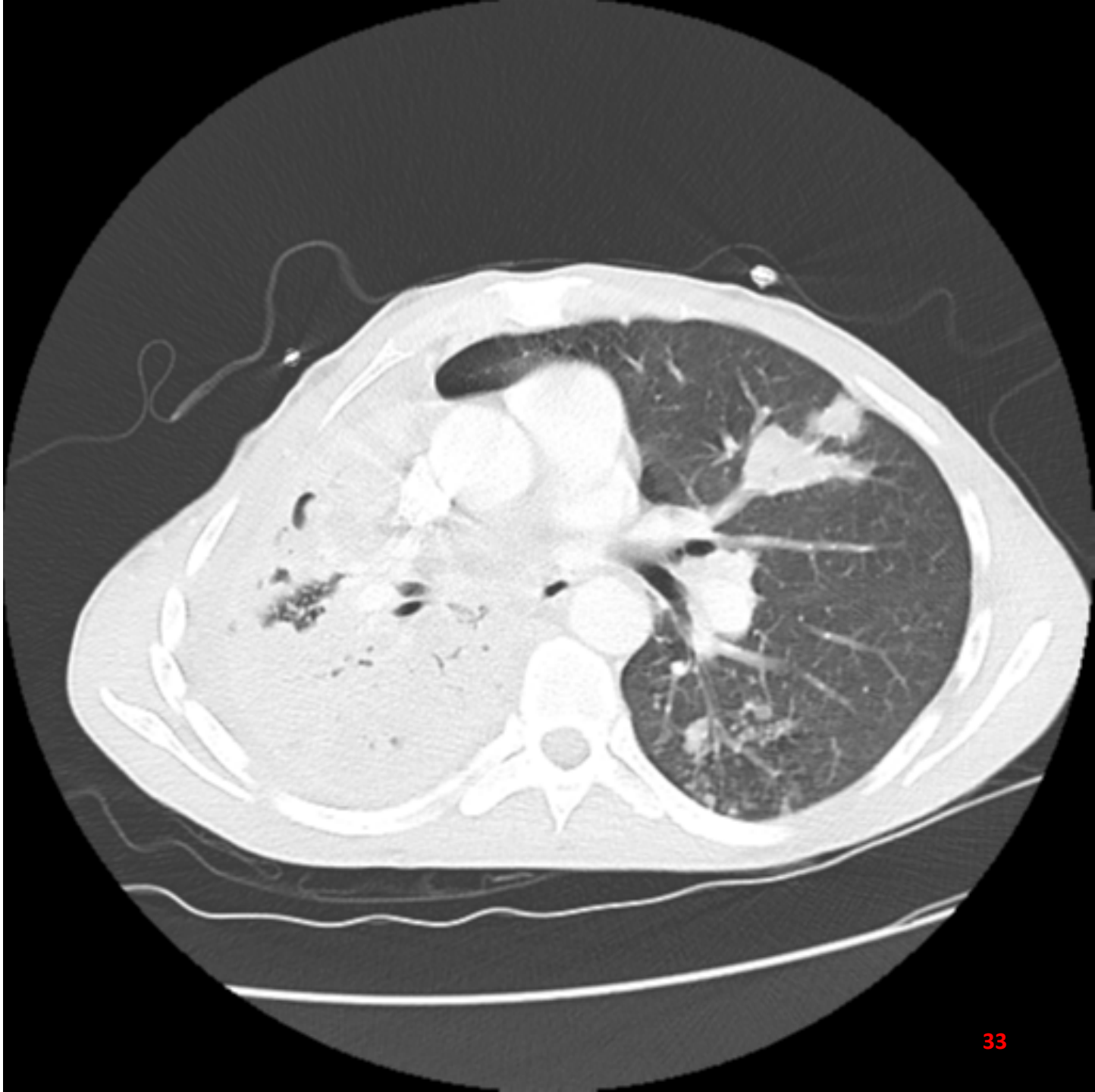

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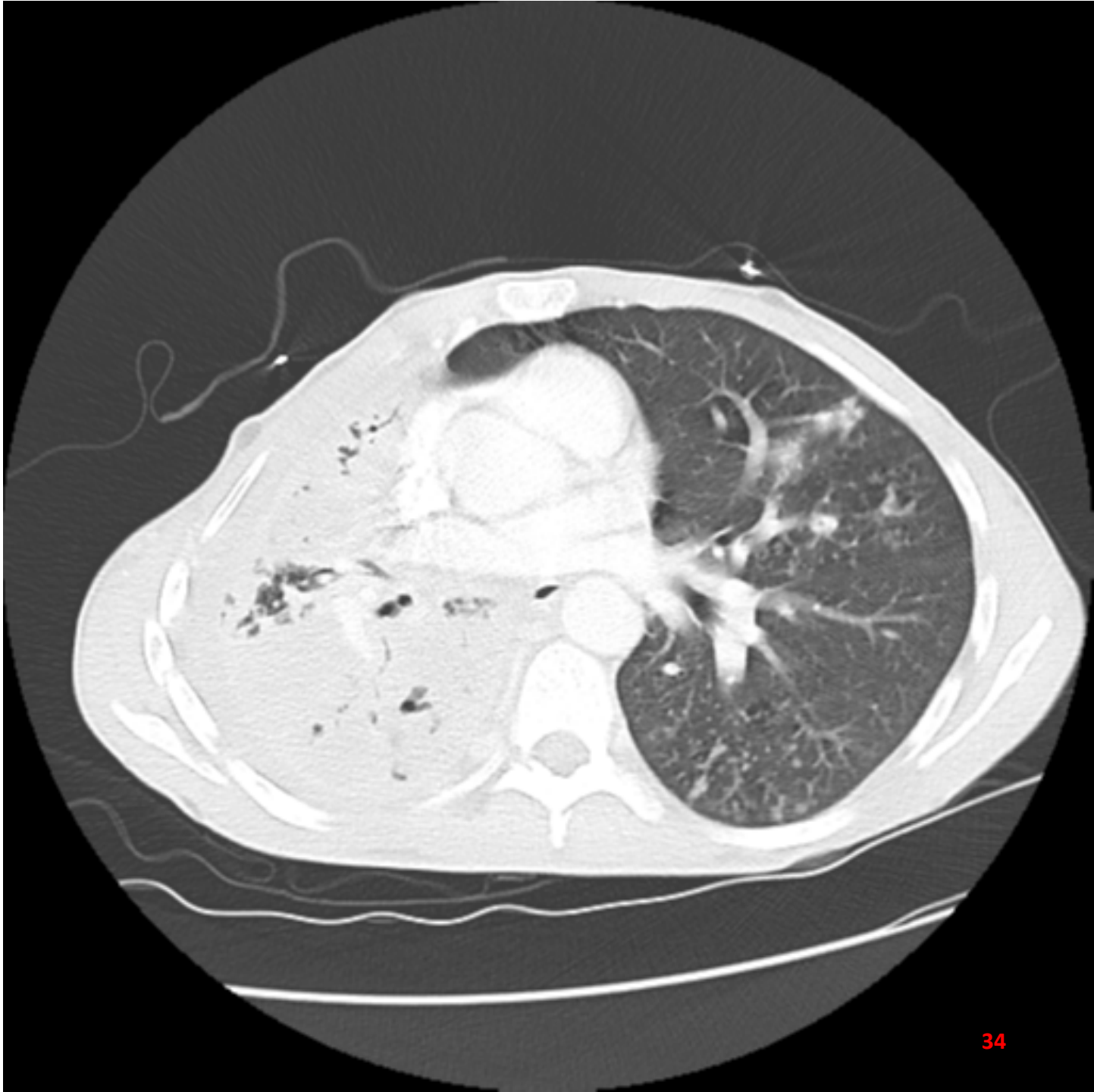

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w/ contrast

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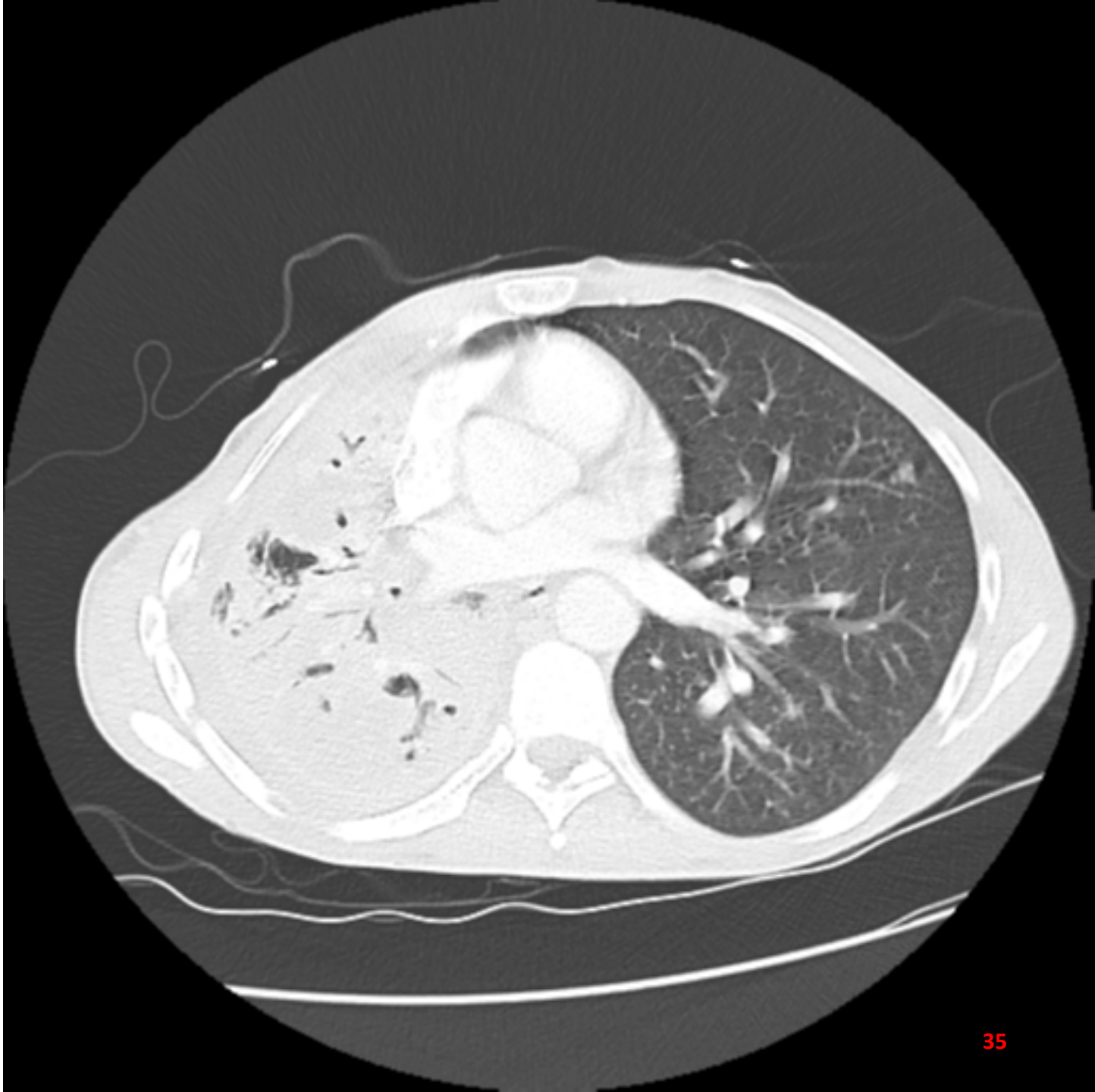
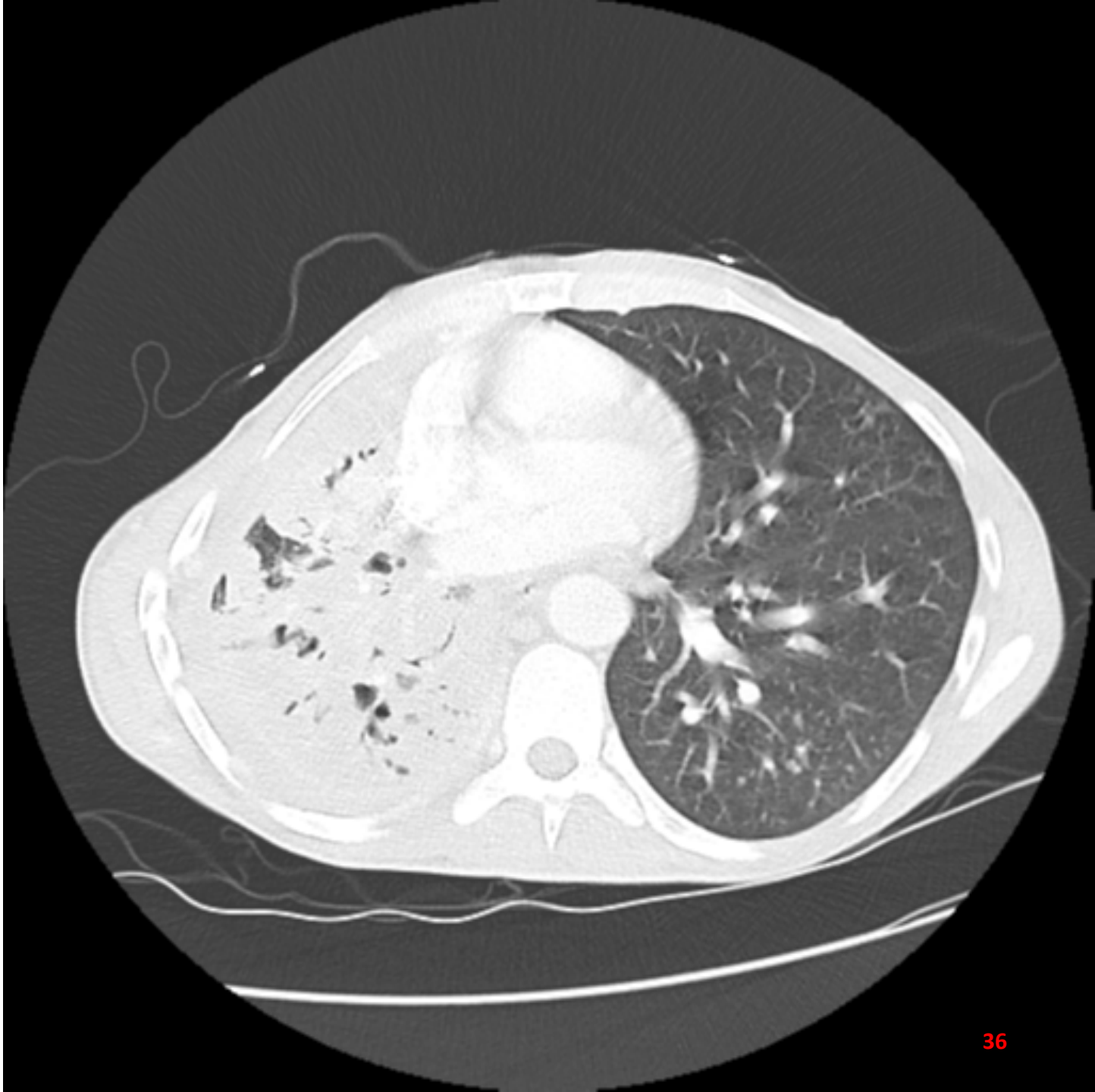


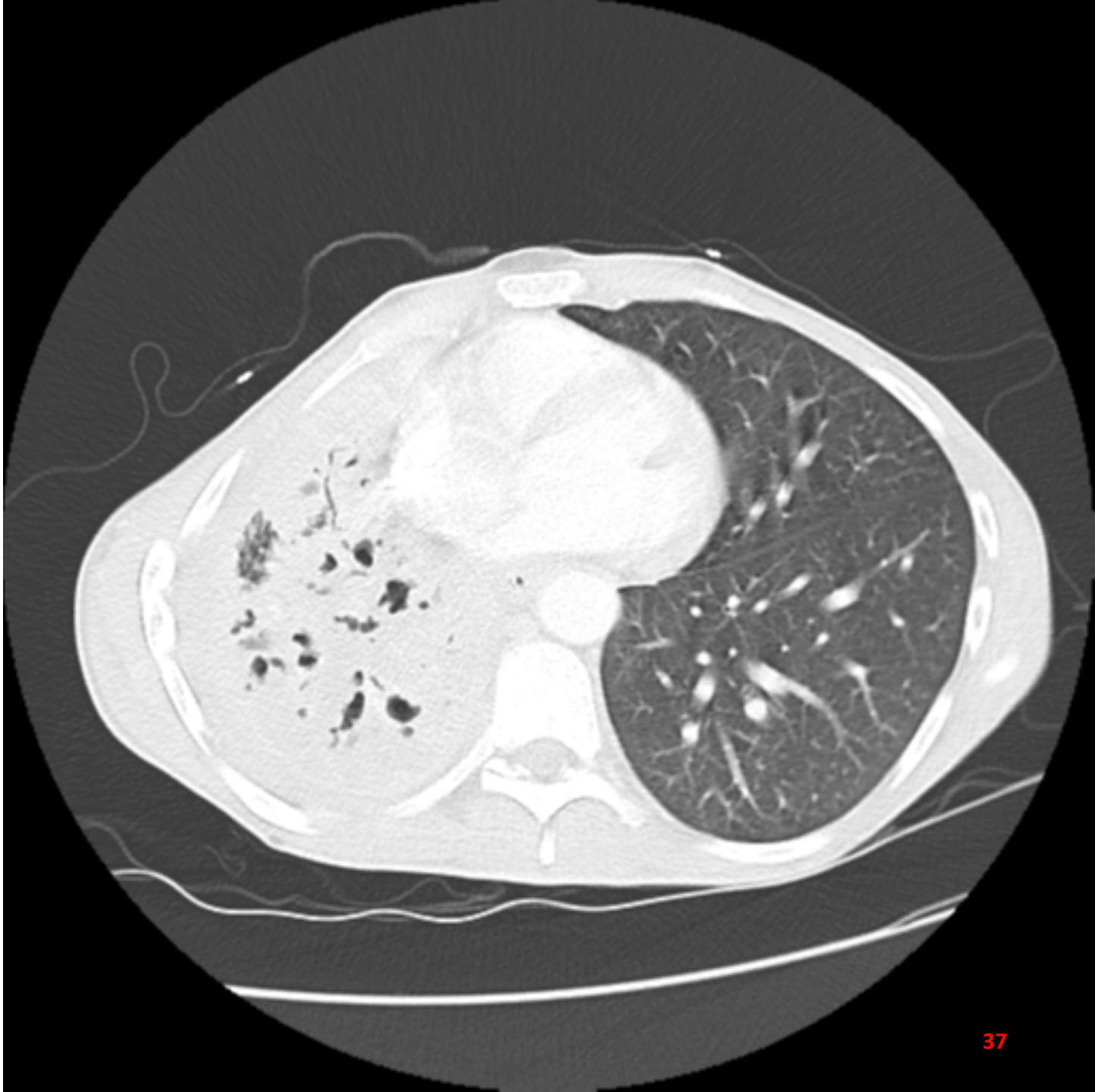
8/26/2019
Chest CT
w/ contrast

36



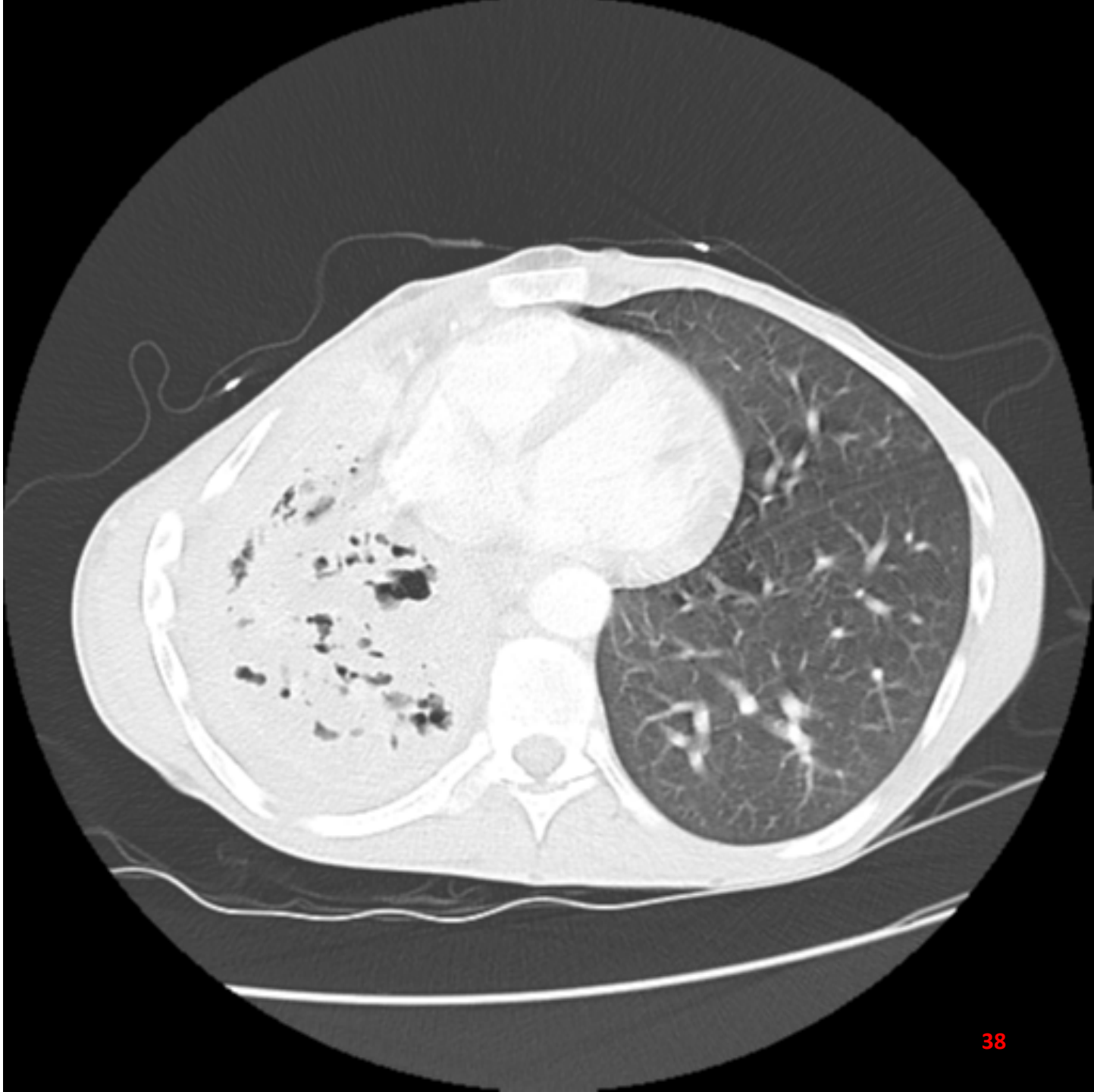
8/26/2019
Chest CT
w/ contrast

38



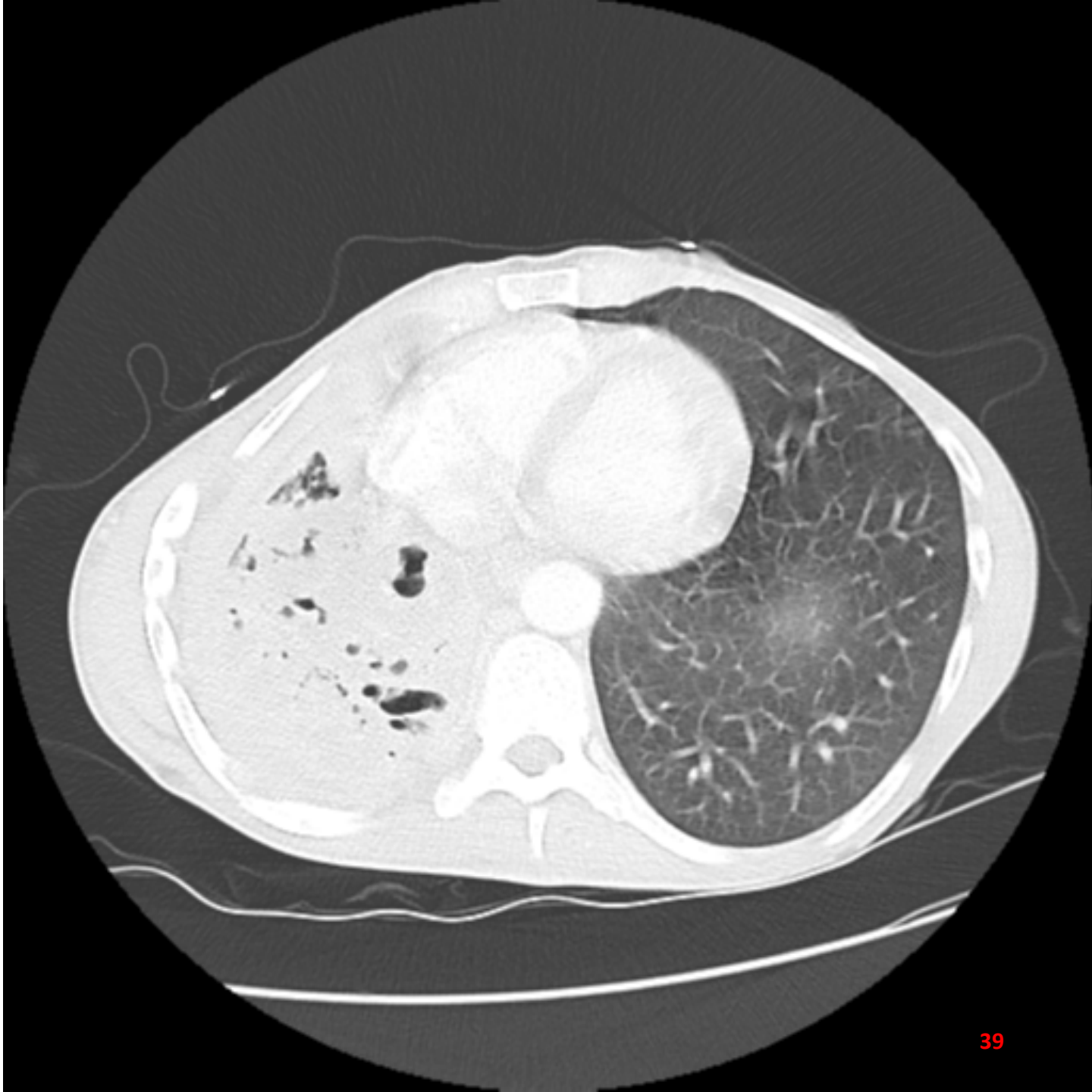
8/26/2019
Chest CT
w/ contrast

40



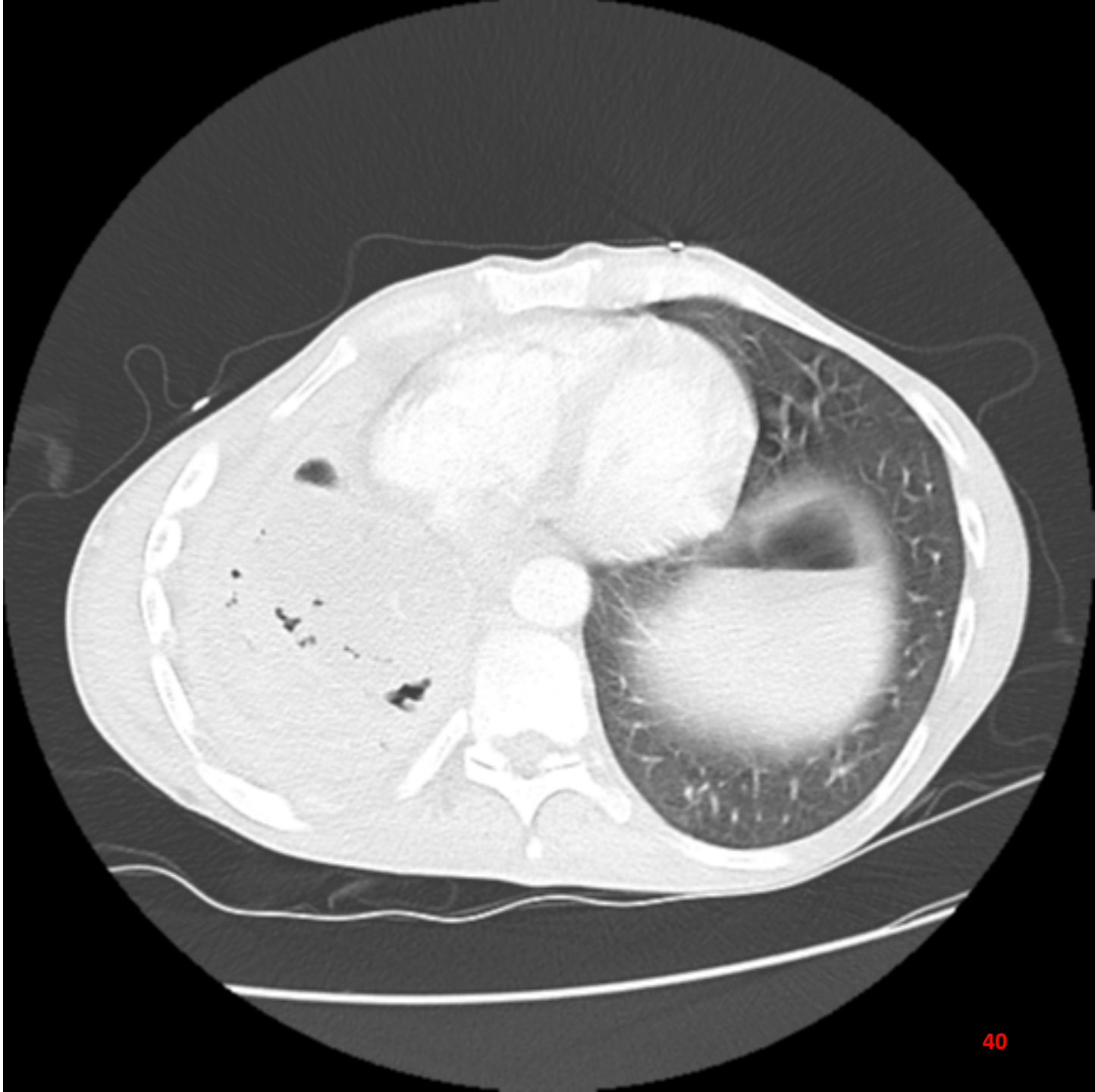
8/26/2019
Chest CT
w/ contrast

42



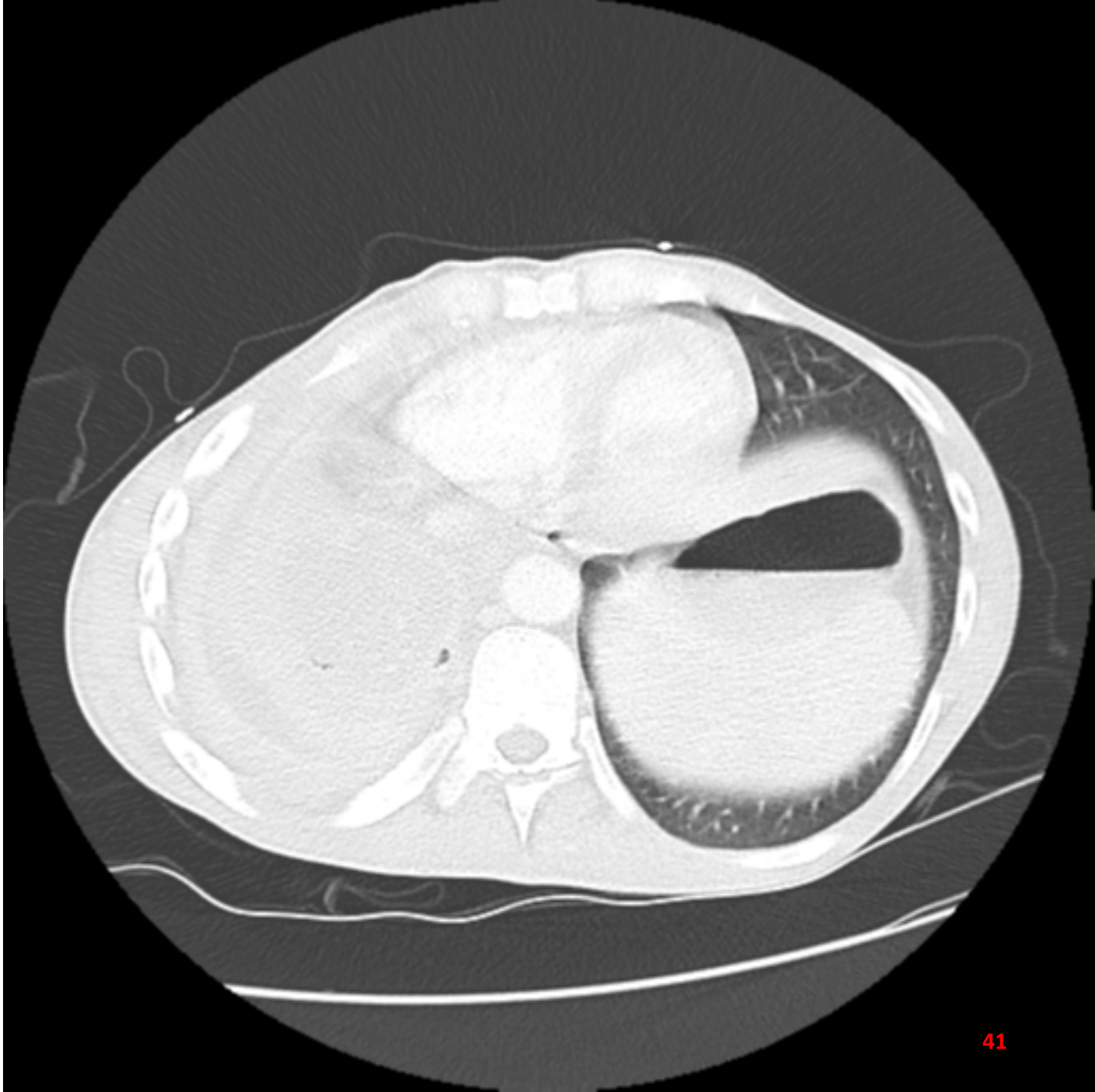
8/26/2019
Chest CT
w/ contrast

44



8/26/2019
Chest CT
w/ contrast

46



The National Goal of "TB Elimination"

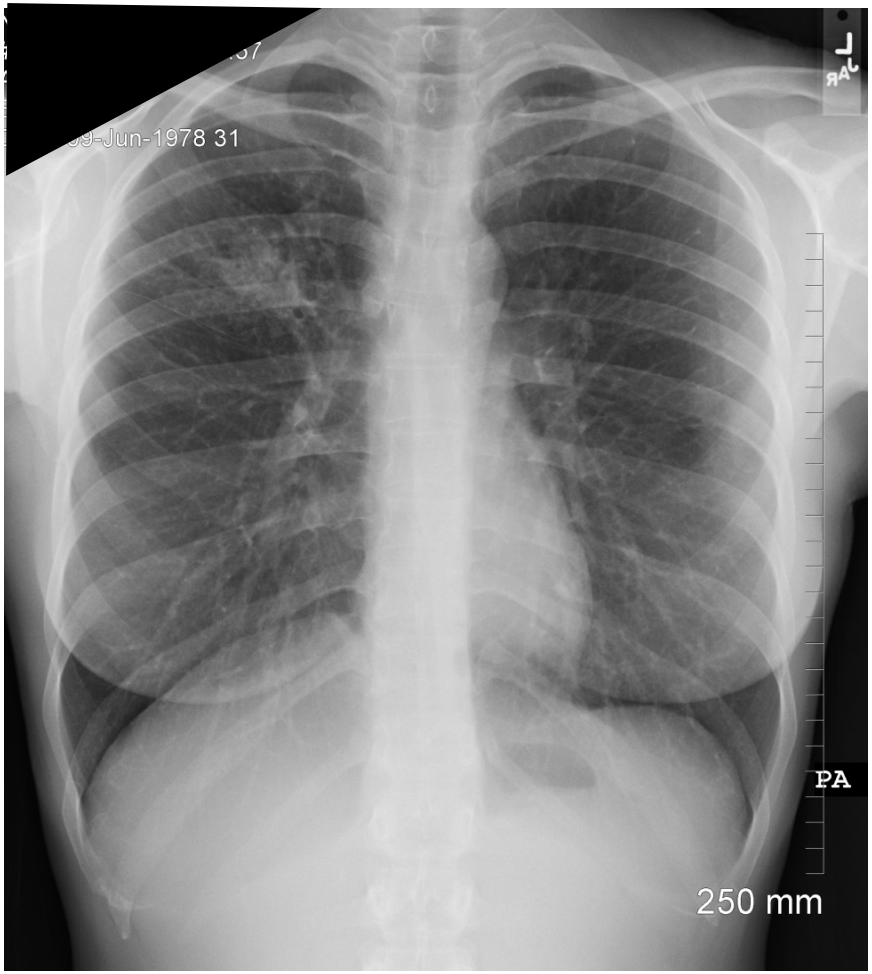
- "TB elimination" vs "TB eradication"
  - < 1 case per million population annually vs zero cases
- Is TB elimination achievable in the U.S.?
- Is TB elimination achievable in Tennessee?
- Key national strategies for achieving TB elimination
  1. Prompt identification, diagnosis and appropriate treatment of TB disease
  2. Identification of close contacts, evaluation and treatment as indicated for those with new TBI
  3. Prevention of TB in populations at high risk for TB

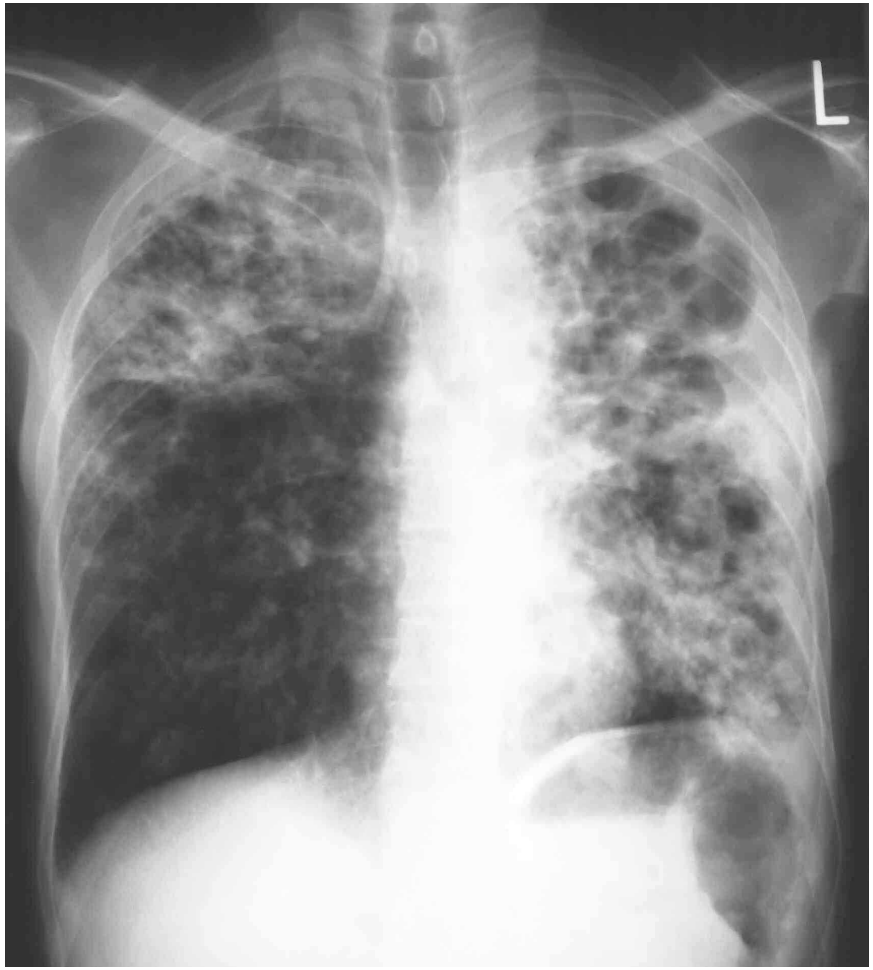
Public health programs alone cannot achieve TB elimination.

Community Parterships to End TB

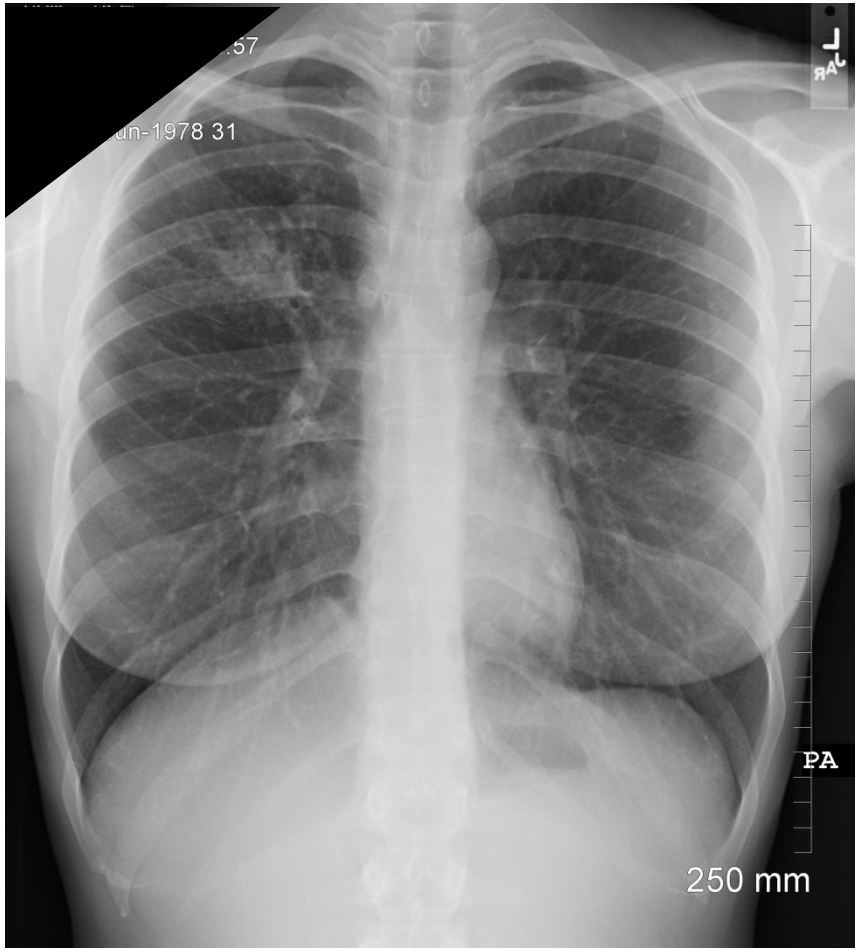
- Collaboration between regional/ local public health agencies and community partner organizations
  - Community TB education, screening, testing and treatment of TBI
  - Primary care providers and practices, community health centers, cultural organizations, etc.
- Identification/ prioritization of populations at risk for TB
  - Quantitative (e.g., epi data, EMR review) and qualitative data
- Considerations
  - Burden of TB disease
  - Access to population at risk
  - Challenges and barriers
  - Resources (known and unknown)
- Political will and commitment for a sustained effort

Pop Quiz: Which is TB disease?





A Cautionary Tale



- 30 y o HCW from TN
- Dx'd with IBD, started on steroids, then TNF-alpha blocker
- Dx'd with CAP, despite tx still symptomatic
- CT-guided biopsy confirms dx of MDR-TB; XDR?
- IV medication x 18+ mo.
- Volunteered twice in AIDS hospice in South Africa

Thank you!

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