

September 2019 Pulmonary Case of the Month: An HIV Patient with a Fever

William Diehl, DO
Nicholas Villalobos, MD

Department of Internal Medicine
University of New Mexico
Albuquerque, NM USA

History of Present Illness

A 33-year old transgender male to female presented from human immunodeficiency virus (HIV) clinic for two months of fevers, intermittent shortness of breath, cough with blood streaked sputum, headache, and nausea. The clinic provider was concerned when labs showed up trending HIV viral load (3.3 million copies) and an absolute CD4 count of 57.

Past Medical History, Social History and Family History

The patient had a history of stage-III HIV diagnosed in 2014 on bictegravir, emtricitabine, tenofovir (Biktarvy) and latent tuberculosis (TB) diagnosed 2017 on isoniazid and B6. She is from Nicaragua and arrived in Albuquerque, NM in 2017. Social history is pertinent for sex trafficking and methamphetamine use.

Physical Examination

Upon admission, the patient's vital signs were notable for a temperature of 39.2 degrees Celsius, blood pressure of 114/71 mmHg, oxygen saturation of 95% on room air with a respiratory rate of 18 breaths per minute. Physical exam was notable for an absence of rash, palpable lymphadenopathy or cachexia.

Which of the following **should be done**?

1. Blood cultures
2. Lumbar puncture
3. Sputum for AFB and tuberculosis
4. 1 & 3
5. All of the above

Correct!
5. All of the above

The patient is an immunocompromised host with a fever of unknown origin and no clear indication from the history and physical examination as to the source of the fever. The reasoning for the blood cultures and sputum for AFB and tuberculosis culture is relatively straight forward and most would do a lumbar puncture because of the headache.

Below is the laboratory evaluation:

CBC

- White blood cell count of 8.1×10^3 cells/uL
- Hemoglobin of 10.9 gm/dL
- Hematocrit of 31%
- Platelet count of 252×10^3 /uL

Chemistry

- Creatinine of 1.24 mg/dL
- Bicarbonate 23 mmol/L
- Anion gap 7 mmol/L

Viral Serology

- Positive Mycoplasma IgM

Cerebrospinal Fluid

- RBC 575 cells
- total nucleated cell count 0 cells
- glucose 44 mg/dl
- total protein 46 mg/dl
- Negative Herpes Simplex Virus and enterovirus polymerase chain reaction (PCR)
- negative gram stain

Induced Acid Fast Bacilli Culture + Stain

- 3/3 no detection of mycobacterium with PCR
- Culture and Stain pending at 14 days.

Blood cultures no growth, preliminary.

Erythrocyte Sedimentation Rate 79 mm/hr

C-Reactive Protein 5.9 mg/dL

Lactate 1.4 mmol/L

Her chest Computerized Tomography (CT) is shown below.

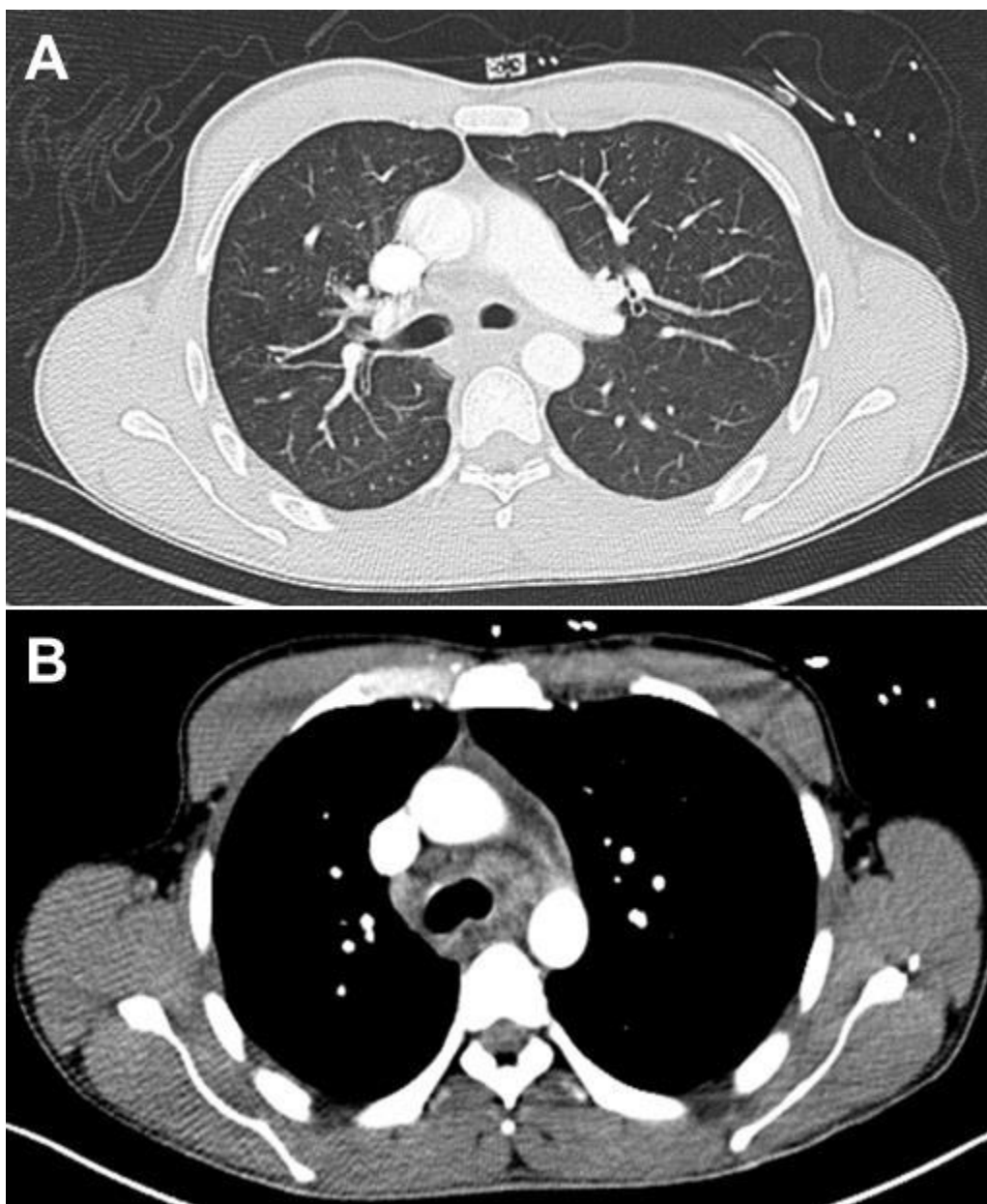


Figure 1. Thoracic CT in lung windows (A) and soft tissue windows (B).

Given the results of the preliminary laboratory tests and chest CT what **disease are you most concerned** with at this time?

1. Active Tuberculosis (TB)
2. Cryptococcus
3. Nontuberculous mycobacterium disease
4. Pulmonary Kaposi sarcoma and/or lymphoma and/or lung cancer
5. Sarcoidosis

Correct!
1. Active Tuberculosis (TB)

The patient has mediastinal lymphadenopathy and all of the above answer choices are potential etiologies for intrathoracic lymphadenopathy in patients with HIV. Given the patient's history of latent TB, cough, duration of symptoms, and history of homelessness the best answer is active tuberculosis.

The differential for intrathoracic lymphadenopathy in patients with HIV includes: mycobacterial disease, nontuberculous mycobacterium disease, bacterial/fungal infection, sarcoidosis, and malignancy (1). Intrathoracic lymphadenopathy in HIV-infected patients is a common finding, in a study by Jasmer *et al.* (2) 35% of HIV-infected patients undergoing chest CT were found to have intrathoracic lymphadenopathy. Opportunistic infections were present in 60% of patients having intrathoracic lymphadenopathy on chest CT (2). Differentiating tuberculosis from lymphoma can be difficult but there are a number of clinical and radiographic predictors (Table 1).

Table 1. Predictors of mycobacterial disease.

Disease	Radiographic Predictors	Clinical Predictors	Highest Odds Ratio (OR)
Mycobacterial disease	<ul style="list-style-type: none">• Necrosis of lymph nodes.• Nodules <1cm.• Cavitation of lymph nodes.	<ul style="list-style-type: none">• Homelessness• Fever• Cough• Night sweats	<ul style="list-style-type: none">• Cough OR 7.4• Chest CT scan showing necrosis of lymph nodes OR 26.4
Lymphoma	<ul style="list-style-type: none">• Absence of pulmonary nodules	<ul style="list-style-type: none">• Less likely homeless• No weight loss• No fever• No cough• No dyspnea	<ul style="list-style-type: none">• Absence of cough OR 125• Symptoms >7 days OR 43.5• Absence of pulmonary nodules OR 20

Radiographic and clinical predictors of mycobacterial disease include: homelessness, fever, cough, night sweats, necrosis of lymph nodes, nodules <1cm, cavitation (2). Factors associated with the highest likelihood of tuberculosis and/or nontuberculous mycobacterium include: cough OR 7.4 and chest CT scan showing necrosis of lymph nodes OR 26.4 (2). Radiographic and clinical predictors of lymphoma include: less likely homeless, no weight loss, no fever, absence of cough OR 125, no dyspnea, symptoms >7 days OR 43.5, absence of pulmonary nodules OR 20 (2). The patient was subsequently started on broad spectrum antibiotics while awaiting cultures and placed in a negative pressure room.

Given the patients lymphadenopathy and history what would be your **next step** to establish a diagnosis?

1. Chest MRI
2. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)
3. Endoscopic ultrasound with fine needle aspiration (EUS)
4. Percutaneous biopsy
5. Positron emission tomography (PET) with fused CT

Correct!

2. Endobronchial ultrasound-guided trans-bronchial needle aspiration (EBUS-TBNA)

Chest MRI is useful for evaluation of large anterior mediastinal masses. PET would be correct if there was a high suspicion for lymphoma or there was need for further identification of a biopsy location. Percutaneous biopsy is useful for lesions distant to airways or located in the anterior or posterior mediastinal compartments. EUS often does not allow for biopsy of the stations 2 and 4R which are often involved in TB. Due to this patient's paratracheal lymphadenopathy EBUS with biopsy is the ideal choice.

For undiagnosed intrathoracic lymphadenopathy in HIV patients, EBUS-TBNA has a diagnostic yield of 77% (3). In one study of HIV patients with intrathoracic lymphadenopathy, the most common lymph node stations involved were 7, 4R, and 11L (3). These results were comparable to findings of Navani *et al.* (4) in which 7 and 4R were the most common nodal stations involved.

The patient was consented and EBUS was performed with multiple lymph node station biopsies including station 7 shown below (Figure 2). Acid fast sputum results were 3/3 negative, few acid fast bacilli were seen on smear and mycobacterium tuberculosis complex was detected by PCR of station 7.



Figure 2. EBUS showing lymphadenopathy with heterogeneous appearance in station 7.

Does the diagnostic yield of acid fast sputum smear and nucleic acid amplification **vary with cluster differentiation (CD)4 count?**

1. No.
2. Yes.

Correct!
2. Yes

The sensitivities of TB testing vary depending on the CD4 count (Table 2, 5).

Table 2. Sensitivities of TB testing with low (< 200 mm³) and high (> 200 mm³) CD4 counts.

	CD4 < 200/mm ³	CD4 > 200/mm ³
Positive tuberculin skin test reaction (> 5 mm without BCG)	30%	50%
Acid-fast bacilli on smear	56–60%	50–58%
Acid-fast bacilli on biopsy	60–65%	50–56%
Granuloma in biopsy	60–75%	67–100%
Mycobacteraemia	20–49%	0–7%

Nucleic acid amplification is 95.5% sensitive for positive sputum smears and 70% sensitive for negative sputum smears (5).

Now that the presumptive diagnosis of TB has been made, therapy should be initiated.

Since the patient has HIV and has been on isoniazid monotherapy since 2018 what **medication adjustments** must you make?

1. No changes are necessary.
2. Rifampin, isoniazid, pyrazinamide, ethambutol, Biktarvy.
3. Rifampin, pyrazinamide, ethambutol, levofloxacin, continue Biktarvy.
4. Rifampin, pyrazinamide, ethambutol, streptomycin, continue Biktarvy.
5. Rifampin, pyrazinamide, ethambutol, levofloxacin, hold Biktarvy for four weeks.

Correct!

5. Rifampin, pyrazinamide, ethambutol, levofloxacin, hold Biktarvy for four weeks.

The patient has been on Isoniazid for treatment of latent TB. Due to active symptoms and paratracheal lymphadenopathy, there would be a high suspicion for isoniazid resistance. When there is clinical suspicion for isoniazid resistance, isoniazid should be held and a fluoroquinolone should be started (6). The most common mechanism of resistance to isoniazid is inhA and katG. Biktarvy should be held up to four weeks while initiating TB therapy to decrease the risk of immune reconstitution inflammatory syndrome (IRIS). IRIS is paradoxical worsening of preexisting infectious processes such as TB. In a secondary analysis of the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) trial, restarting anti-retroviral therapy (ART) in the first four weeks of tuberculosis treatment was associated with a two-fold higher incidence of IRIS (7).

References

1. Fishman J and Sagar M. Spectrum Diagnosis. AIDS Patient Care STDS. 1999;13(11):645-9. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Jasmer RM, Gotway MB, Creasman JM, Webb WR, Edinburgh KJ, Huang L. Clinical and radiographic predictors of the etiology of computed tomography-diagnosed intrathoracic lymphadenopathy in HIV-infected patients. J Acquir Immune Defic Syndr. 2002;31(3):291-8. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Prasad KT, Muthu V, Sehgal IS, *et al.* Utility of endobronchial ultrasound-guided transbronchial needle aspiration in HIV-infected patients with undiagnosed intrathoracic lymphadenopathy. Lung India. 2018;35(5):173-5. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Navani N, Molyneaux PL, Breen RA, *et al.* Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study. Thorax. 2011;66(10):889-93. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Aaron L, Saadoun D, Calatroni I, *et al.* Tuberculosis in HIV-infected patients: a comprehensive review. Clin Microbiol Infect. 2004;10(5):388-98. [\[CrossRef\]](#) [\[PubMed\]](#)
6. WHO. WHO treatment guidelines for drug-resistant tuberculosis. World Health Organization. 2016:1-30. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Naidoo K, Yende-Zuma N, Padayatchi N, *et al.* Immune reconstitution inflammatory syndrome following antiretroviral therapy initiation in tuberculosis patients: findings from the SAPiT trial. NIH Public Access. 2013;18(5):1199-1216. [\[CrossRef\]](#) [\[PubMed\]](#)