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Cases of Infection in the Immunocompromised Host

Stephanie Levine MD and Lisa Moores MD

Disclosures

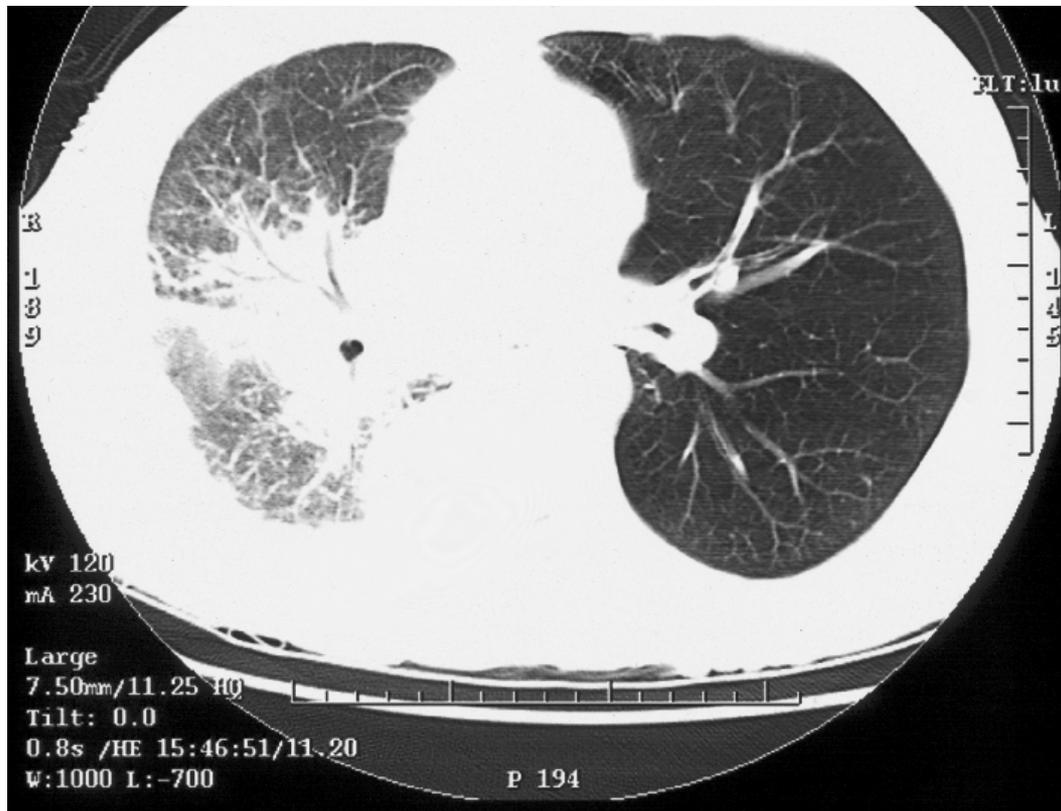
- Nothing to disclose

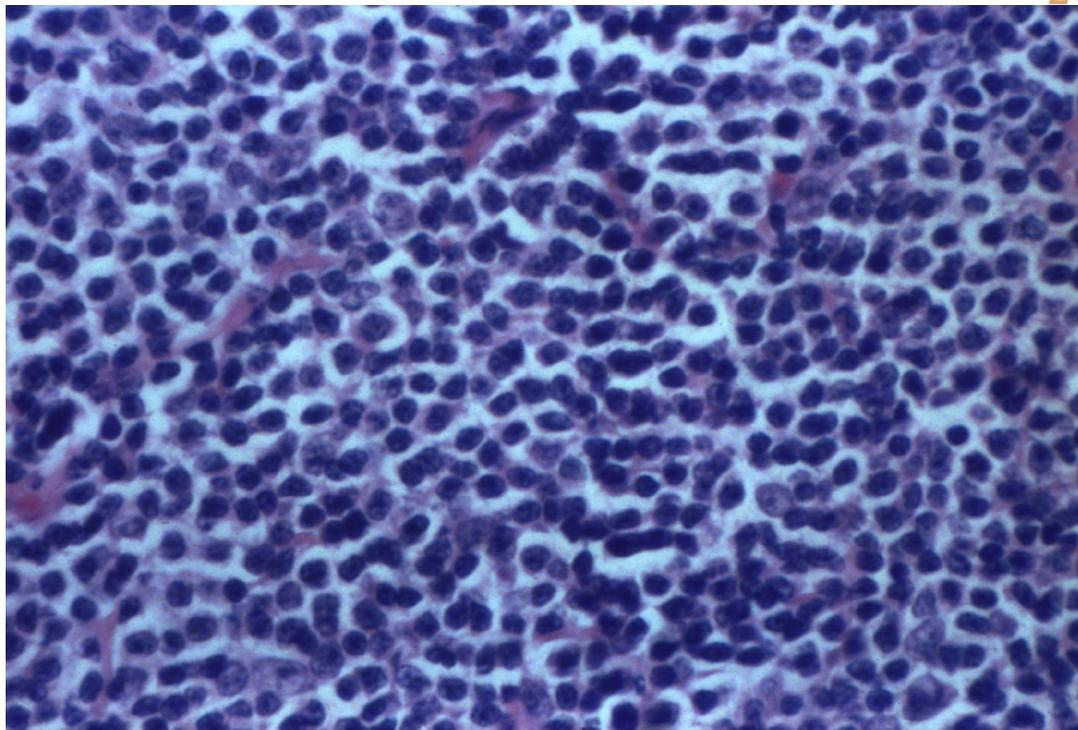
Case 1

- 60 yo man 13 months s/p right SLT for COPD
- Unremarkable post-LT course
- CMV match
- Note mild DOE, dry cough, intermittent wheezing.
Subjective fevers
- 5% decrease in home spirometry
- Meds- tacrolimus, mycophenolate mofetil, prednisone.
Off Trimethoprim-sulfamethoxazole and valganciclovir.

Case 1

- Afebrile
- Right lung- scattered wheezes
- Left lung- decreased BS
- Labs- unremarkable
- CT
- Bronchoscopy with TBBX. Micro- pnd.
- FEV1 1.4L from 1.55L
- Tacrolimus level- therapeutic





The next best step in his management is:

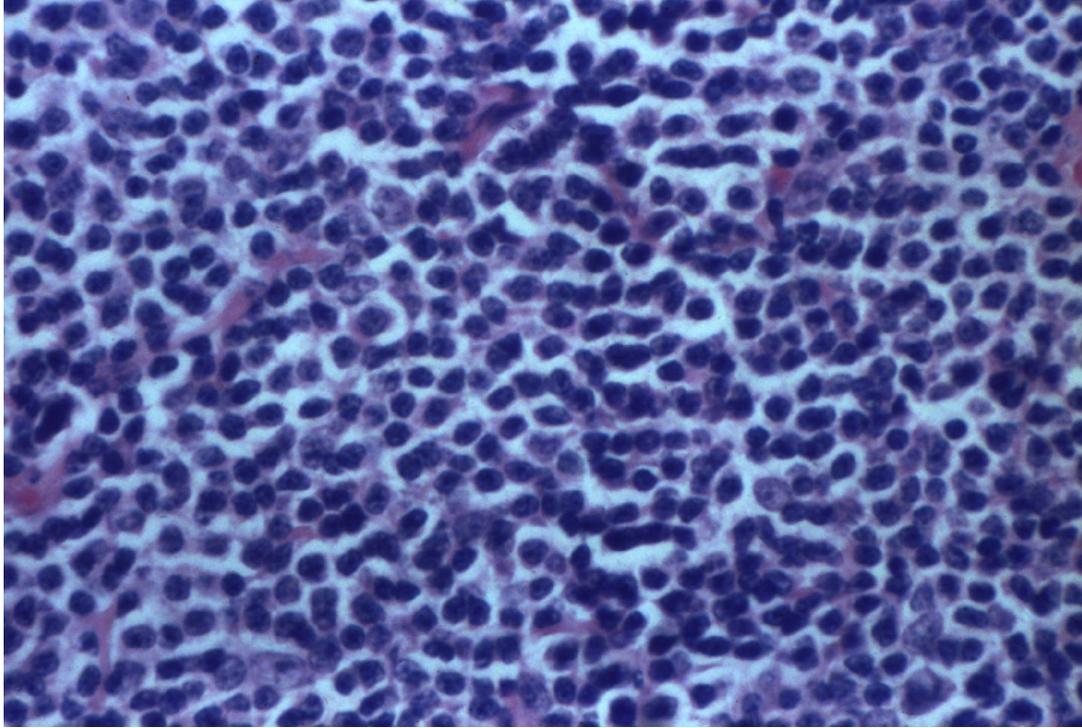
- A. Continue current IS and begin IV ganciclovir
- B. Decrease current IS and begin rituximab
- C. Decrease current IS and begin voriconazole
- D. Continue current IS and begin ceftazidime and ciprofloxacin

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Post-transplant Lymphoproliferative Disorders (PTLD)

- Heterogenous group of lymphoid proliferations of variable clonality
- Increased incidence over other organ transplant groups. 4.6-9.4%.
- B cell
- Non-Hodgkin's
- Associated with EBV- seroconverters, children



PTLD

- Clinical presentation
 - Develop in the first posttransplant year
 - Allograft often involved
 - CXR- solid or multiple pulmonary nodules or infiltrates
 - Extrapulmonary involvement- CNS

PTLD

- Treatment
 - Rituximab (CD20 monoclonal Ab)
 - Some reports of complete remission
 - Side effects- few
 - Balance dose and rejection
 - Reduced immunosuppression
 - Antiviral therapy
 - Chemotherapy, radiation, surgery, adoptive immunotherapy

LT Complications

- PTLD
 - highest incidence within the first post-LT year
 - related to **B-cell proliferation by Epstein-Barr virus (EBV)**
- Acute graft rejection
 - Usually within the first 3 months but can occur up to 2 years post-LT
 - Clinical features - nonspecific dyspnea, fever, leukocytosis, nonproductive cough, hypoxemia, or malaise, but can be asymptomatic
 - Diagnosis transbronchial lung biopsy, which reveals **perivascular lymphocytic infiltrates**

The next best step in his management is:

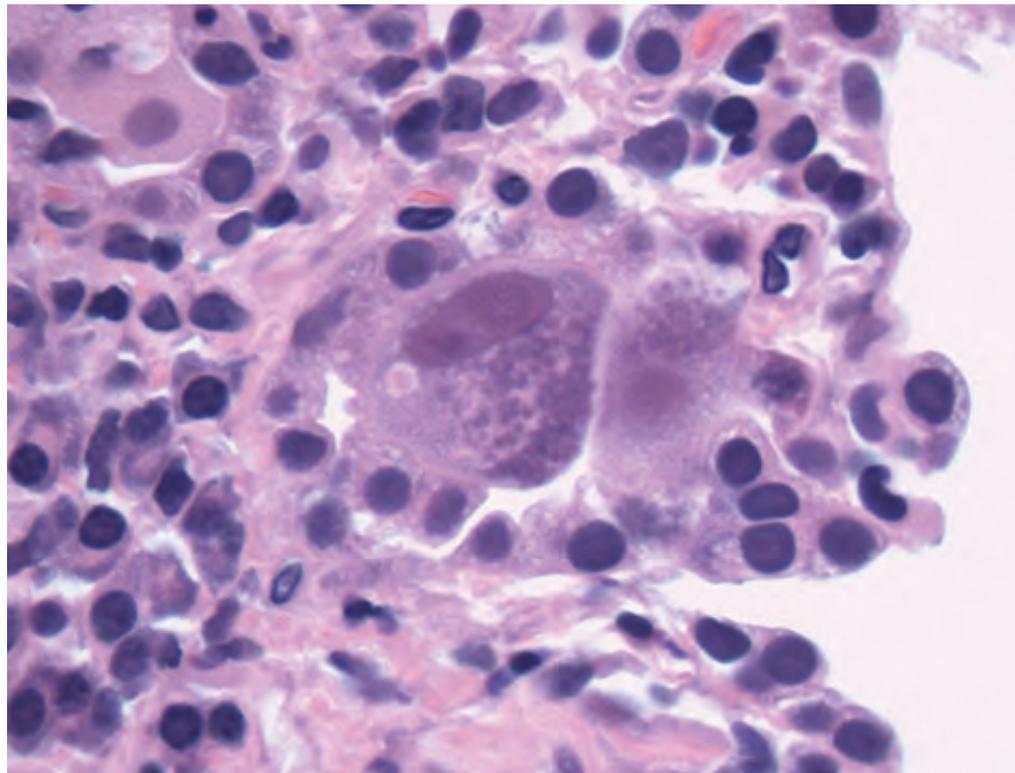
- A. Continue current IS and begin IV ganciclovir – not CMV
- B. Decrease current IS and begin rituximab
- C. Decrease current IS and begin voriconazole-
Not fungal
- D. Continue current IS and begin ceftazidime and ciprofloxacin- not GNR infection

Case 2

- A 57-year-old man underwent bilateral lung transplantation for COPD
- The donor was cytomegalovirus (CMV) antibody-negative, and the recipient was CMV antibody-positive
- His postoperative course was complicated by hemolysis, acute renal failure, and initial weaning difficulties, but he improved and was discharged to a rehabilitation facility 2 months postoperatively.
- Subsequent to that, he remained well with no new pulmonary complaints

Case 2

- His medications included tacrolimus, prednisone, mycophenolate mofetil, valganciclovir (planned for 3 months) and trimethoprim-sulfamethoxazole three times weekly
- He underwent routine surveillance transbronchial biopsies to monitor for rejection at 1 and 2 months after discharge, and no abnormalities were noted
- Monthly monitoring of his blood for CMV antigen had been negative postoperatively, currently pnd
- A routine surveillance transbronchial biopsy done 4 months after discharge is shown. A representative image from a CT scan done at the same time is shown
- The patient feels good except for mild, occasional cough and sputum, and results of a physical exam are normal



Case 2

The abnormalities demonstrated are most likely due to:

- A. Posttransplant lymphoproliferative disease
- B. Acute rejection
- C. Cytomegalovirus infection
- D. *Pneumocystis jirovecii* infection

Case 2

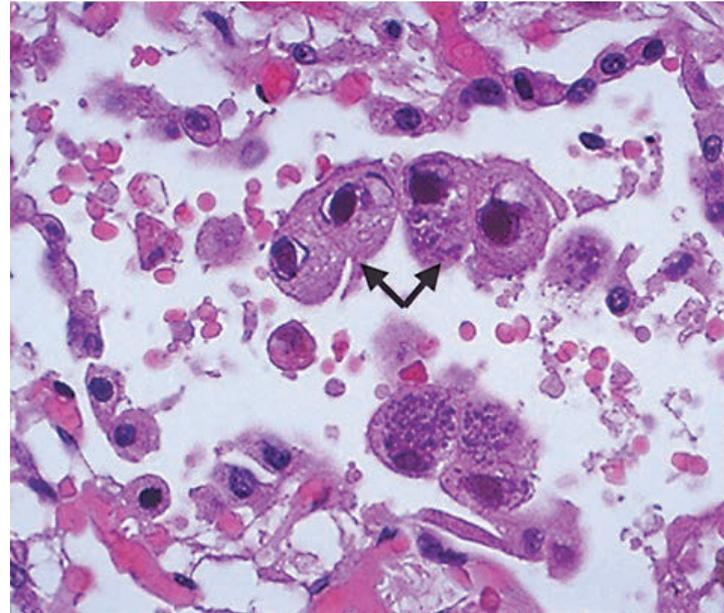
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Cytomegalovirus Infection

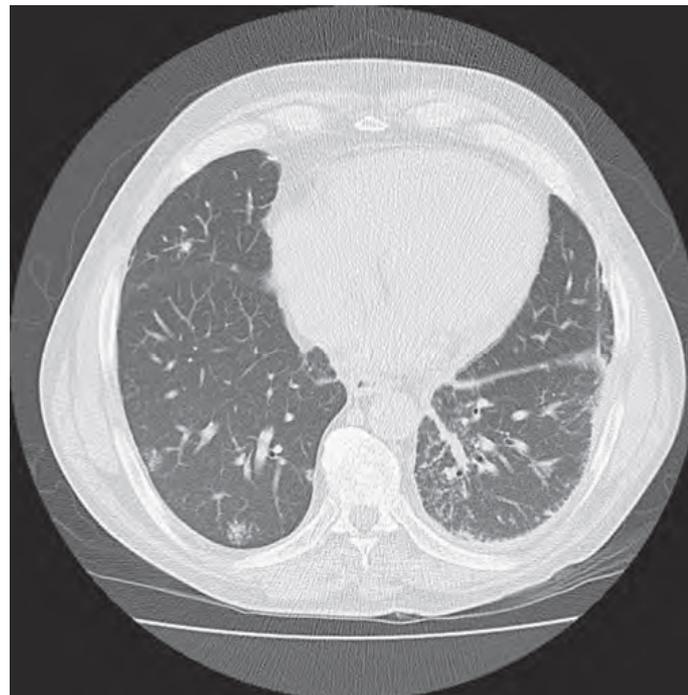
Pathology

- Intranuclear inclusion bodies with the classic “owl eyes”
- Markedly enlarged (cytomegalic) cells with large amphophilic (purple) intranuclear inclusions and multiple small basophilic (blue) intracytoplasmic inclusions



CMV

- CT scan- micronodules
- Interlobular septal thickening



CMV

- Immunosuppression peaks at 1 to 6 months after transplant
- Opportunistic infections from viral (CMV), *P jirovecii*, Aspergillus or Candida spp
- CMV infection associated with development of bronchiolitis obliterans and chronic allograft dysfunction
- The most severe infections occur due to primary infections in donor-positive, recipient-negative patients

- Secondary CMV infection occurs with reactivation of latent disease, which is unmasked with immunosuppression
- CMV most commonly causes pneumonitis, but it may also present as retinitis, hepatitis, colitis, or gastroenteritis
- Monitoring - serial measures of CMV polymerase chain reaction (PCR) or antigenemia in the blood

CMV Treatment

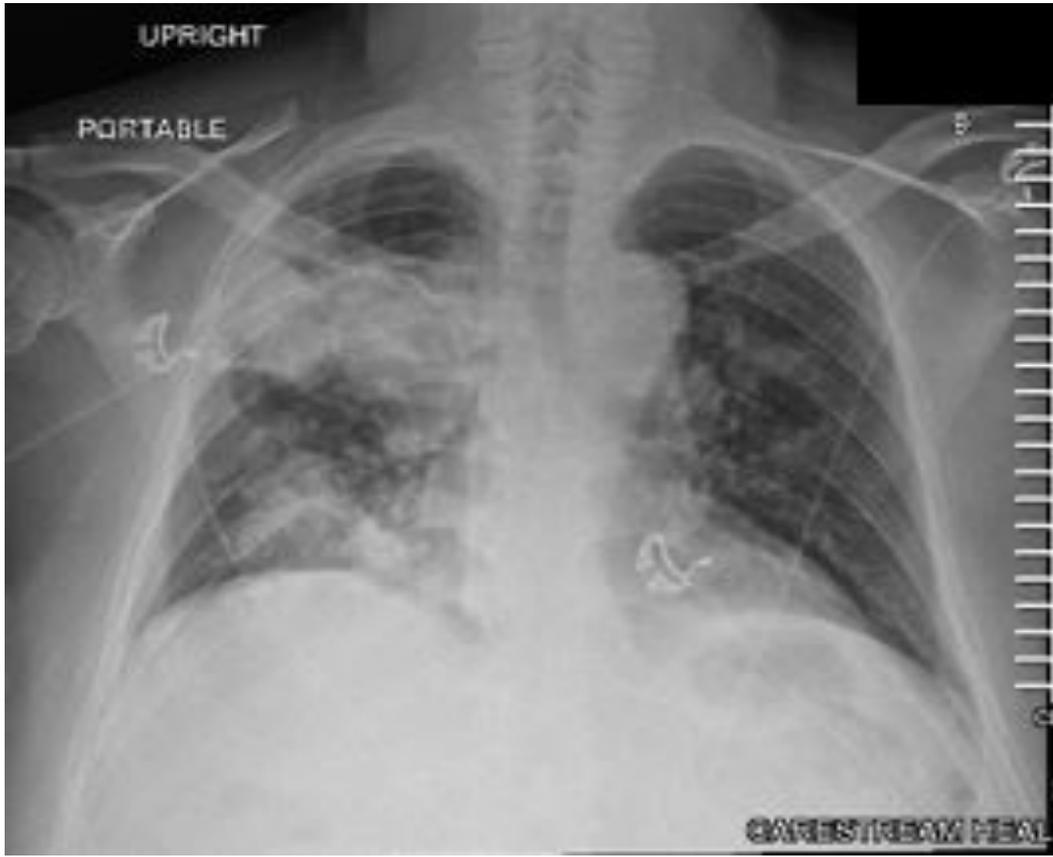
- IV ganciclovir or oral valganciclovir
- CMV prophylaxis (duration varies)
 - recipient-negative, donor-positive individuals- longer, maybe lifelong
 - recipient-positive individuals (including the current patient) –variable but usually > 1 year
 - recipient and donor-negative individuals- shorter and may use acyclovir
 - concerns about resistance

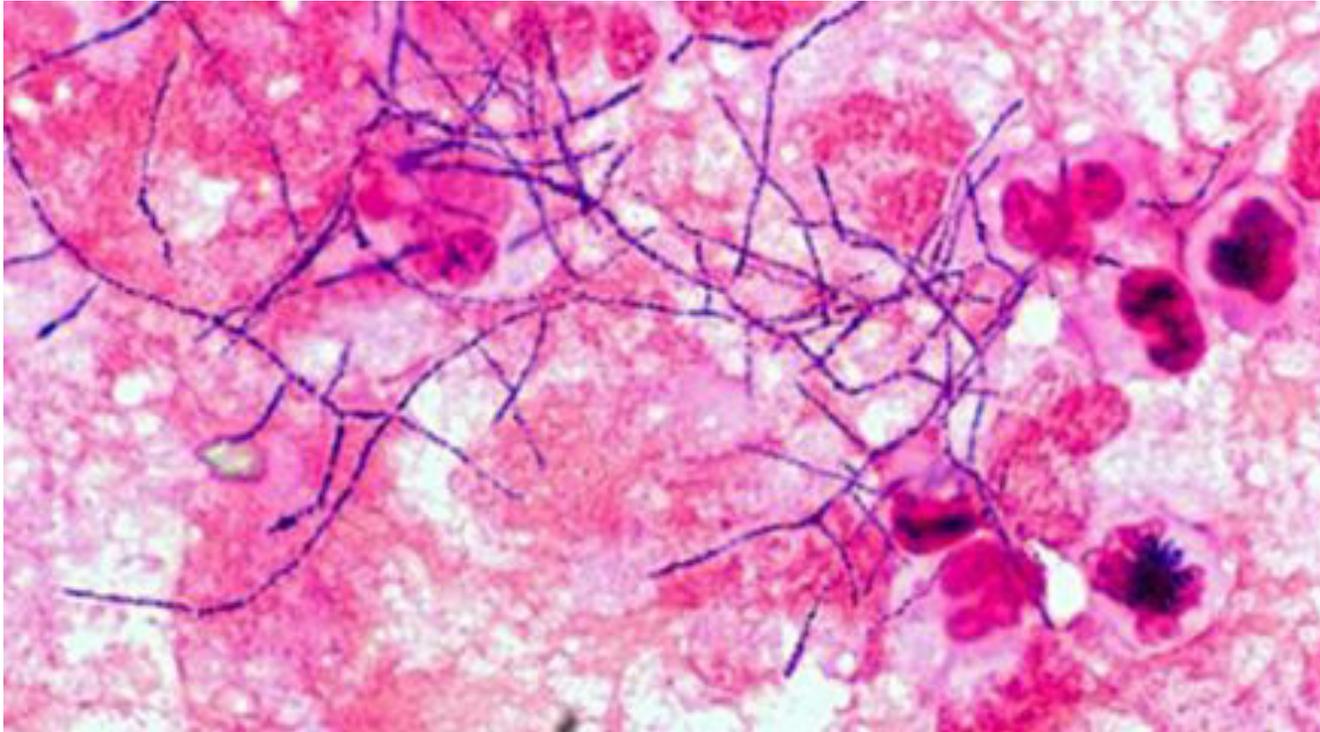
Case 3

- A 36-year-old man who had a liver transplant for hepatitis C 8 years ago is seen in an outlying emergency clinic for 3 days of increasing shortness of breath, mildly productive cough, low grade fevers, and night sweats and is prescribed a 7 day course of levofloxacin
- He comes to the ED 2 weeks later with continued symptoms and intermittent headaches
- Medications include prednisone, tacrolimus, mycophenolate mofetil, and prophylactic trimethoprim-sulfamethoxazole orally three times/week (TIW) and valganciclovir daily. There are no known drug allergies

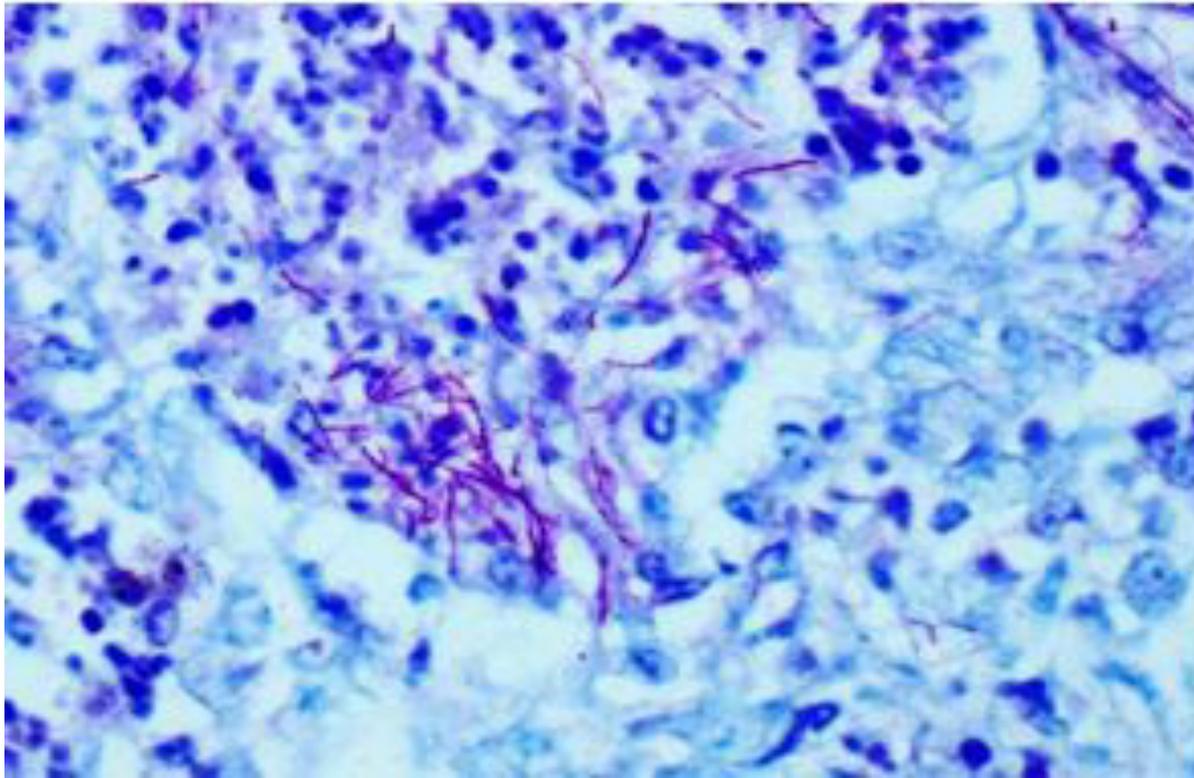
Question 3

- On examination his temperature is 38.3°C (101°F), pulse is 90/minute, respiratory rate is 20/minute, and BP is 120/80 mmHg. Room air oxygen saturation is 88%. Dentition is poor. Lungs reveal egophony in the posterior right upper lung field, and the remainder of the examination is unremarkable
- The chest radiograph is shown. A head CT is normal
- White blood cell count is 10,000/ μl ($10 \times 10^9/\text{L}$)
- One dose of vancomycin and cefepime are given and he is admitted and undergoes bronchoscopy with bronchoalveolar lavage (BAL), and sterile brush with the BAL gram stain and AFB stain shown
- Cultures and sensitivities for bacterial, fungal and mycobacterial organisms are pending





Gram stain



AFB stain

What is the likely diagnosis?

- A. *Pseudomonas aeruginosa*
- B. Nocardia
- C. Actinomycosis
- D. *M. tuberculosis*

What is the likely diagnosis?

- A. *Pseudomonas aeruginosa*
- B. **Nocardia**
- C. Actinomycosis
- D. *M. tuberculosis*

What should be done at this time?

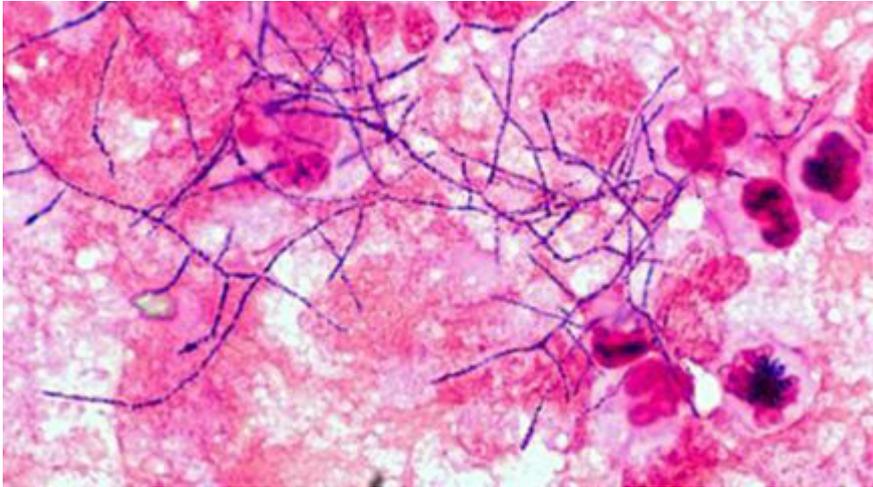
- A. Begin piperacillin-tazobactam
- B. Change TIW oral trimethoprim-sulfamethoxazole to daily IV and add amikacin
- C. Change TIW oral trimethoprim-sulfamethoxazole to daily IV
- D. Begin rifampin, isoniazid, pyrazinamide, ethambutol and azithromycin

What should be done at this time?

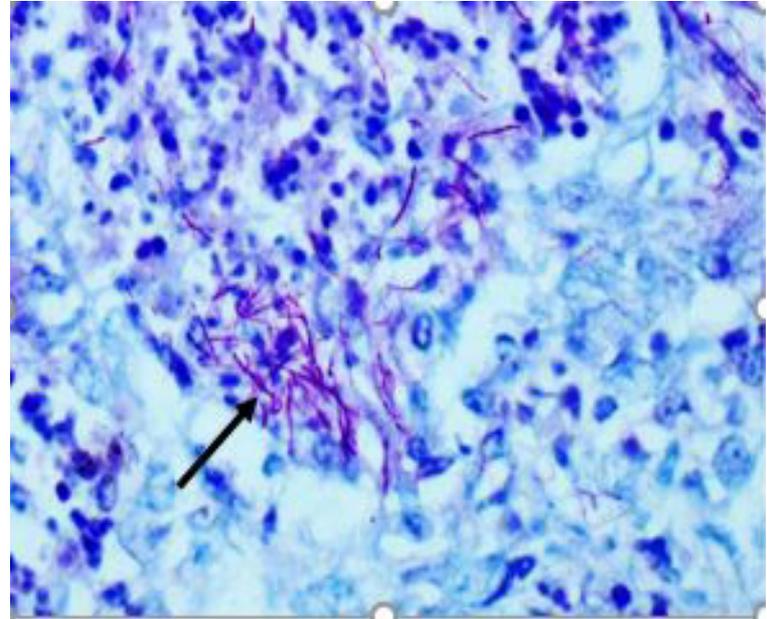
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Nocardia

- Caused by an aerobic, gram positive organism
- Opportunistic infection; immunocompetent patients in about 1/3 of cases
- Localized or systemic with predisposition to dissemination particularly to the central nervous system
- Can relapse or progress even on appropriate antibiotic treatment



Gram stain



AFB stain

Nocardia- Epidemiology/ Clinical Findings

- Found worldwide
- Mode of acquisition - usually inhalational, but cutaneous routes and ingestional routes of entry are described
- Risk factors - cell mediated immunocompromise, such as the use of corticosteroids, chemotherapy, underlying malignancy, diabetes, HIV infection and solid organ and hematopoietic cell transplant recipients (highest in first year)
- Pulmonary infection is the most common manifestation in organ transplant recipients- lung and heart transplant recipients (3.5% and 2.5% respectively), liver and kidney recipients (0.1% and 0.2% respectively)

Nocardia- Clinical Findings

- Systemic with >2 sites involved in 32% of cases
- Single organ involvement- pneumonia (39%), CNS (9%), skin (8%), others - bone 12%
- Pneumonia - chronic or subacute with fever, sweats, weight loss, dyspnea, and cough. Hemoptysis may be seen.
- Fifty percent of pulmonary cases can disseminate usually to the CNS.
- Radiographic findings- consolidation, nodular and mass like infiltrates (single or multiple and with or without cavitation), reticulonodular or interstitial infiltrates, and pleural effusion
- In the CNS - brain abscesses with headache, fever, focal neurologic findings and /or seizures, or asymptomatic

Nocardia- Diagnosis

- Pulmonary- stains, cytology and culture of the sputum, BAL, or transbronchial biopsy.
- BAL - Gram stain and modified AFB stain and culture
- Growth may be delayed (5-21 days) so let laboratory be aware
- Cultures positive in tissue in up to 90% of cases.
- *Nocardia asteroides* common species
- Pathology- necrosis with microabscess formation.
- All immunocompromised patients - brain CT or MRI also those with immunocompetency and anything other than cutaneous disease

Nocardia- Treatment

- Sulfonamides such as trimethoprim-sulfamethoxazole (TMP-SMX), first line after susceptibility testing is available
- Amikacin, imipenem, third generation cephalosporins, linezolid
- Amoxicillin-clavulanic acid or minocycline (mild cases)
- Mild-moderate pulmonary nocardiosis in the immunocompetent host- TMP-SMX
- Severe infection, and /or CNS involvement- two or three intravenous agents while susceptibility testing is pending, TMP-SMX plus amikacin or with imipenem for CNS disease
- TMP-SMX- good penetration into the CSF
- 2-16% of isolates may be resistant to TMP-SMX and formal susceptibility testing needed
- In immunocompromised patients with moderate to severe disease but without CNS involvement, IV TMP-SMX plus amikacin while awaiting sensitivities, or imipenem plus amikacin

Nocardia- Treatment

- Oral therapy- not appropriate for initial treatment in immunocompromised patient with pneumonia
- After three- six weeks of IV therapy, and depending on the response, and sensitivity results, treatment can be switched to oral therapy usually high dose TMP-SMX.
- Treatment - for 6-12 months, (12 months in the immunocompromised)
- Chronic immunosuppression- lifelong indefinite secondary prophylaxis
- For sulfa allergy- desensitization is recommended

What should be done at this time?

- A. Begin piperacillin-tazobactam- not agent of choice, good for Actinomycosis (sulfur granules, not AFB positive)
- B. Change TIW oral trimethoprim-sulfamethoxazole to daily IV and add amikacin
- C. Change TIW oral trimethoprim-sulfamethoxazole to daily IV- must wait for sensitivities
- D. Begin rifampin, isoniazid, pyrazinamide, ethambutol, and azithromycin- not *M. tuberculosis* or NTM

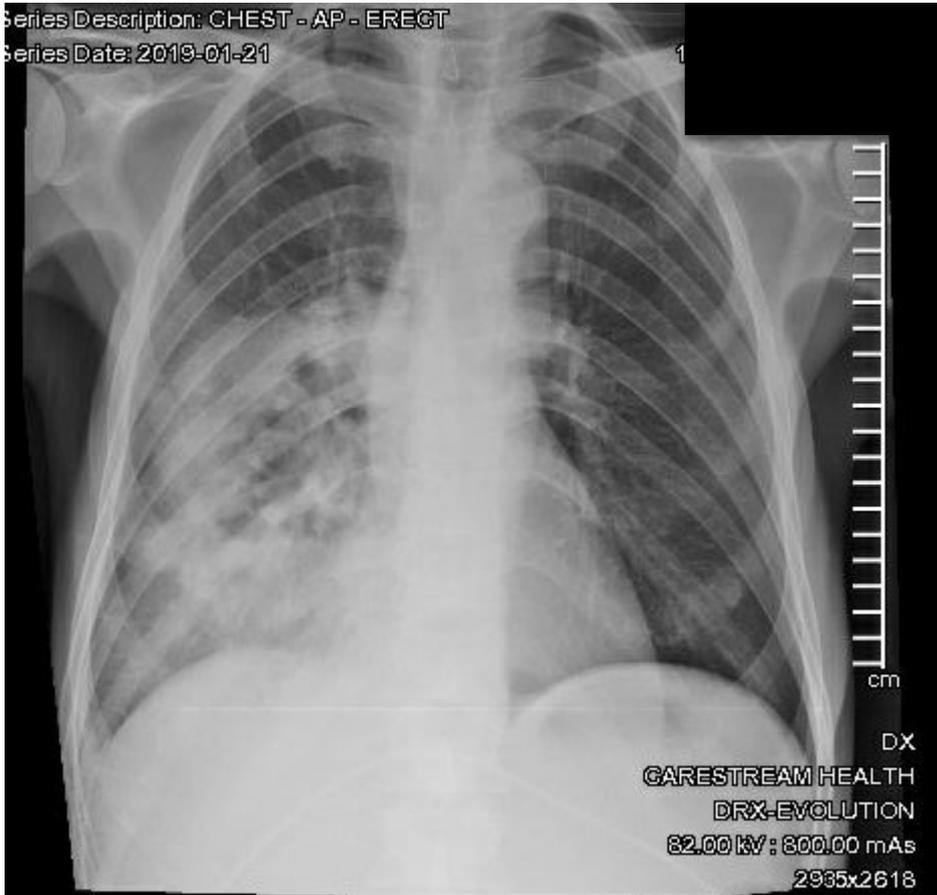
Case 4

- A 50 year-old man with HIV presents with a 1 month history of shortness of breath, fevers, chills, night sweats and a 7 kg weight loss
- He reports cough productive of green sputum with occasional flecks of blood
- He was diagnosed with HIV 10 years prior but is intermittently compliant with anti-retroviral medications

Case 4

- On examination he is chronically ill appearing
- Temp. 39⁰C. Poor dentition, Lungs- RLL egophony and crackles
- Labs
 - WBC 8,000/mm³
 - CD4 < 40 cells/mm³
 - Viral load 25,000

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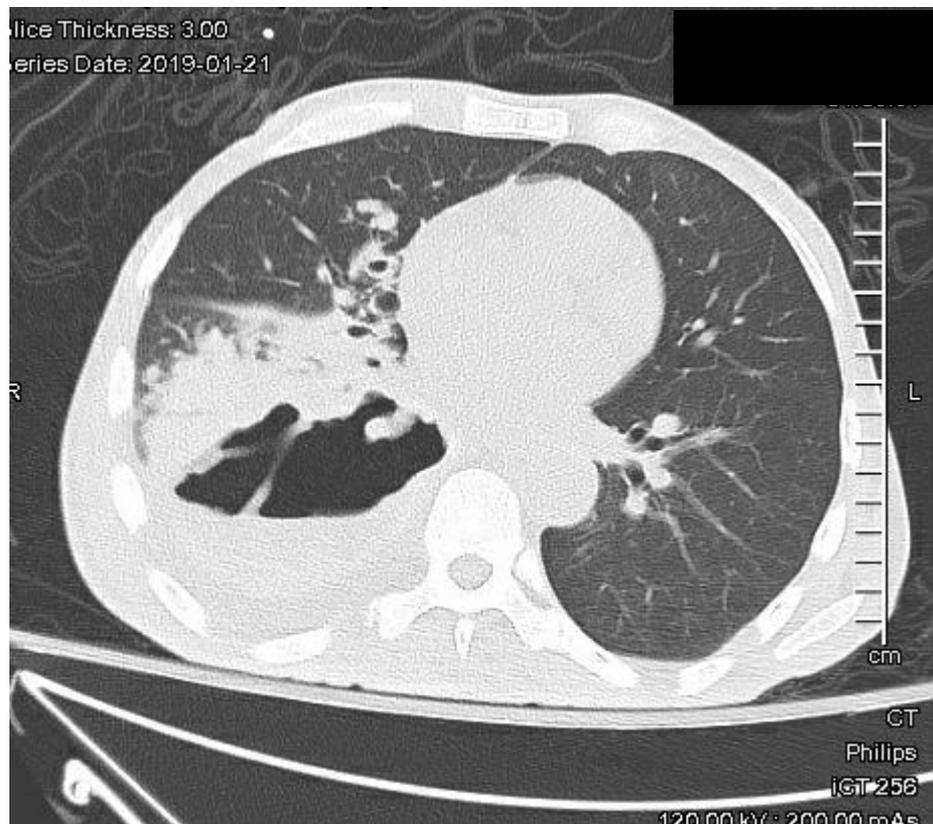


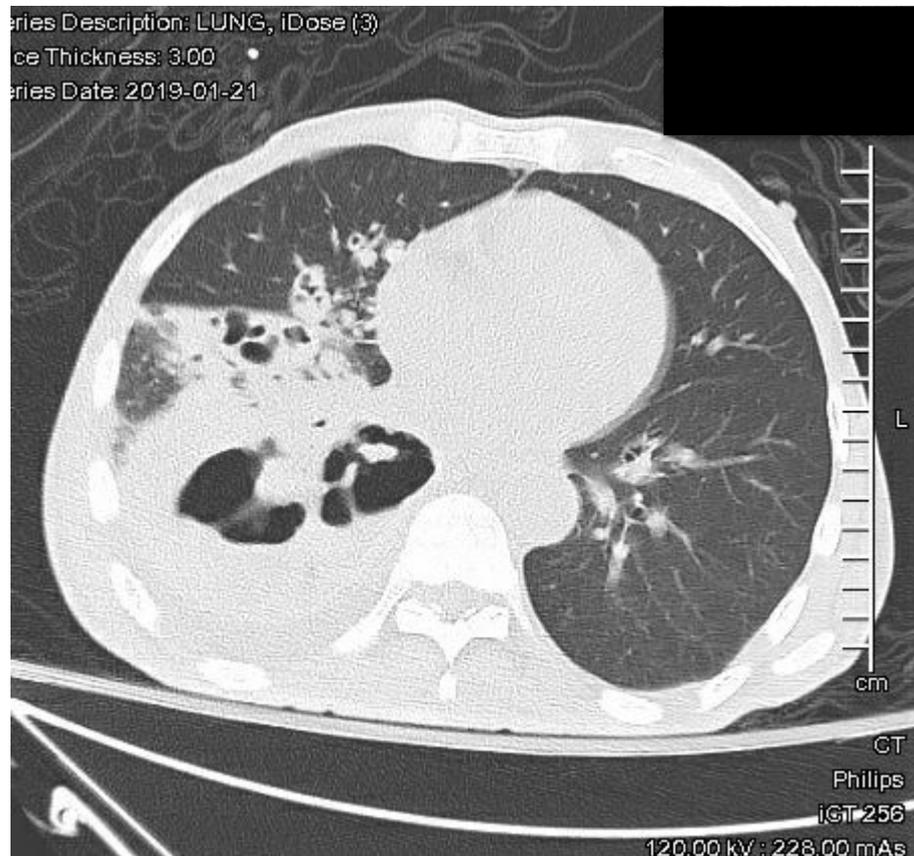
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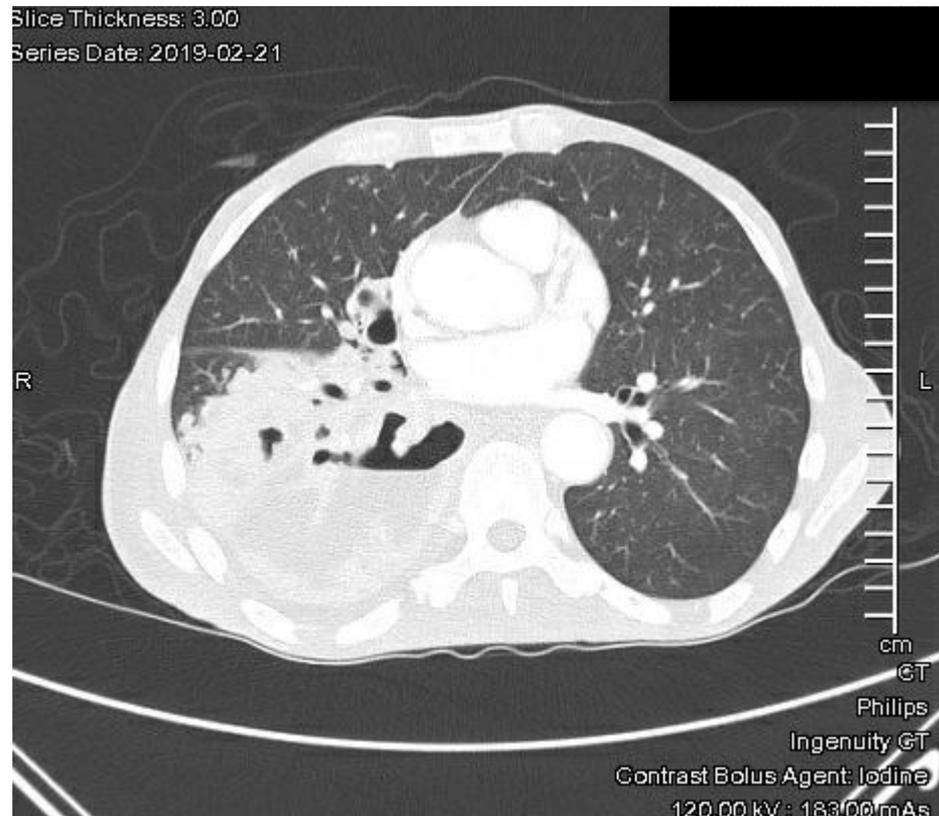


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Case 4- Hospital Course

- He remained febrile despite broad spectrum antibiotics
- Sputum cultures show mixed flora
- Sputum for AFB x 3 were negative
- Blood cultures grew a gram positive coccobacillus organism - not *B. anthracis* on multiple cultures

What is the most likely diagnosis?

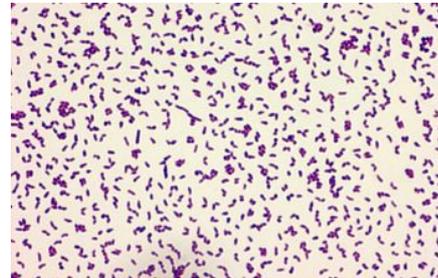
- A. *M. tuberculosis*
- B. *Rhodococcus equi*
- C. Actinomycosis
- D. *Pneumocystis jiroveci*

What is the most likely diagnosis?

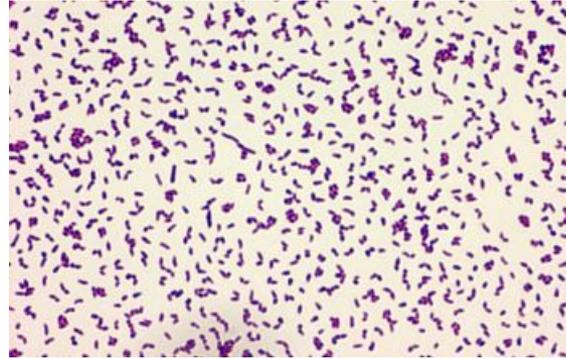
- A. *M. tuberculosis*
- B. *Rhodococcus equi*
- C. Actinomycosis
- D. *Pneumocystis jiroveci*

Rhodococcus equi

- Used to be *Corynebacterium equi*
- As name suggests associated with horses
- Seen in HIV (CD4 counts $< 100 /\text{mm}^3$) and other immunocompromised hosts
- Found in soil
- Inhaled or ingested



Rhodococcus equi



- Gram positive coccobacilli
- May be weakly acid fast
- Clinical- sub-acute- fever, cough, hemoptysis, fatigue, weight loss
- CXR- Nodular infiltrate or consolidation often with cavitation (50%), may have pleural effusion (20%)
- Pulmonary is most common (82%),but extrapulmonary infection can occur- CNS, skin, wounds, lines
- Diagnosis- often made on blood culture in 50% of cases or sputum or bronchoscopy cultures

Rhodococcus equi- Treatment

- Macrolide or quinolone and rifampin
- Macrolide or quinolone and two of:
 - imipenem, vancomycin, linezolid and aminoglycoside
- Usually treat for 2 months and/or until less immunocompromised
- Secondary prophylaxis recommended

What is the most likely diagnosis?

- A. *M. tuberculosis* (AFB negative, culture negative)
- B. *Rhodococcus equi*
- C. Actinomycosis (gram stain not consistent)
- D. *Pneumocystis jirovecii* (imaging characteristics make this less likely)

Case 5

- A 29-year-old man presented to an outpatient clinic with a 2-month history of fever, cough, dyspnea, and weight loss, as well as skin lesions that had developed on his face, neck, trunk, arms, and legs over a period of 2 weeks
- Physical examination revealed extensive umbilicated papules

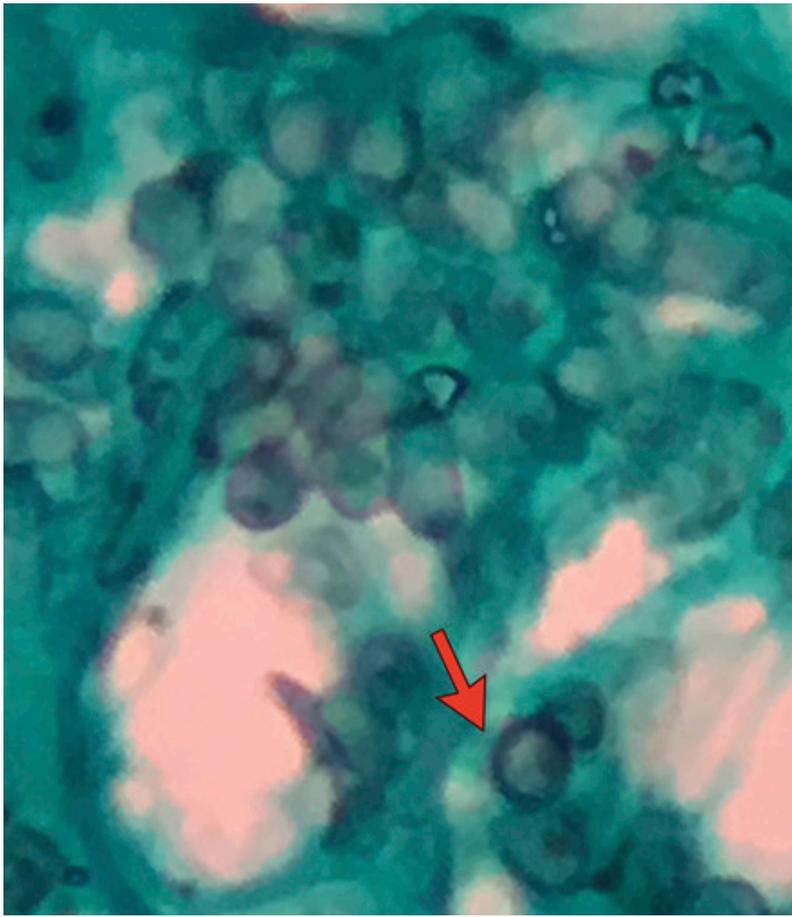


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Biopsy
specimen of
papule;
methenamine
silver stain

Case 5

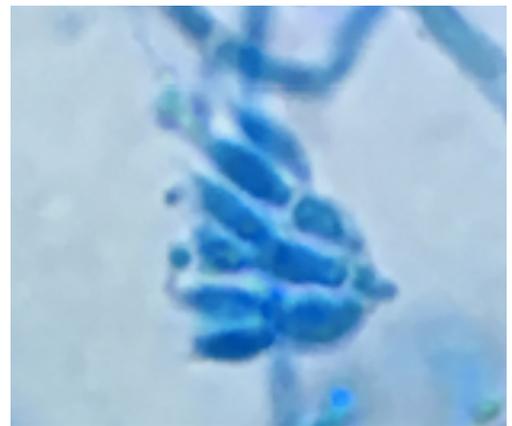
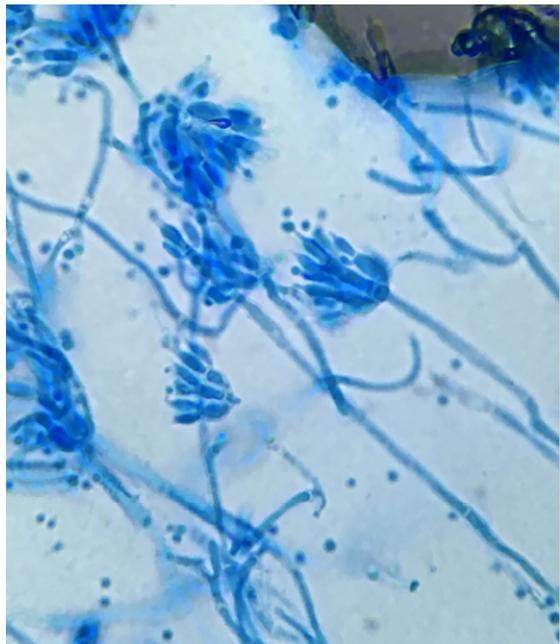
What is the best treatment option?

- A. Rifampin, Isoniazid, Ethambutol and Pyrazinamide
- B. Ceftazidime
- C. Amphotericin B
- D. Trimethoprim-Sulfamethoxazole

Case 5

What is the best treatment option?

- A. Rifampin, Isoniazid, Ethambutol and Pyrazinamide
- B. Ceftazidime
- C. **Amphotericin B**
- D. Trimethoprim-Sulfamethoxazole



Tissue culture grew *Talaromyces marneffeii* (formerly *Penicillium marneffeii*)

Talaromyces

- *Talaromyces marneffe* (formerly *Penicillium marneffe*) is an important cause of morbidity and mortality in HIV-infected and other immunosuppressed patients who live in or are from Southeast Asia
- *Penicillium marneffe* was renamed *Talaromyces marneffe* in 2015, and the disease, which had been referred to as penicilliosis, is now called talaromycosis
- HAART has led to a significant decline
- *T. marneffe* infection continues to cause considerable morbidity and mortality in AIDS patients unaware of their HIV infection, who do not have access to ART, or who have a suboptimal response to HIV therapy

Talaromyces (Penicillium)

- *T. marneffe* a dimorphic fungus that is endemic in southern China, Southeast Asia, and northeastern India
- Causes infection in people with HIV infection who live in these regions
- Incidence of *T. marneffe* infection has decreased with the increased use HAART
- Increasing incidence of infection among other persons with impaired cell-mediated immunity, such as those who have undergone organ transplantation.

Presentation

- Most patients with talaromycosis present with signs and symptoms related to infection of the reticuloendothelial system, including generalized lymphadenopathy, hepatomegaly, and splenomegaly

Clinical manifestations of HIV-infected patients with *Talaromyces (Penicillium) marneffei* infection

	Number of cases (percent)		
	Thailand ^[1] (N = 80)	Vietnam ^[2] (N = 513)	India ^[3] (N = 36)
Fever	74 (92.5)	419 (82)	35 (97)
Weight loss	61 (76.2)	92 (18)	36 (100)
Cough	39 (48.7)	205 (40)	N/A
Abdominal pain	N/A	160 (32)	N/A
Diarrhea	25 (31.2)	150 (30)	8 (22)
Skin lesions	57 (71)	346/487 (71)	29 (81)
Anemia	62 (77.5)	286/397 (72)	31 (86)
Genital ulcer	5 (6.2)	N/A	N/A
Hepatosplenomegaly	41 (51)	286 (56)	14 (39)
Lymphadenopathy	46 (57)	131 (26)	12 (33)

Respiratory Symptoms

- Cough, fever, dyspnea, and chest pain may be present
- Chest radiography can show diffuse reticulonodular, localized alveolar, or diffuse alveolar infiltrates
- Atypical pulmonary presentations have also been reported, including single or multiple cavitary lesions and a lung mass

Diagnosis

- A definitive diagnosis is usually made by culture of the fungus from blood, skin biopsy, bone marrow, or lymph node
 - Cultures of bone marrow and lymph node biopsies most sensitive, followed by skin lesions and blood
- Presumptive diagnosis can be made by demonstrating the characteristic morphologic findings in biopsy material or in blood smears
- Elongated yeast-like organisms with a clearly defined central septum. The presence of a centrally located transverse septum (eg, "cross wall") differentiates *T. marneffe* from *Histoplasma capsulatum*

Diagnosis

- Neither Antigen testing/PCR-based techniques using serum or urine are currently used to diagnose *T. marneffe*. However, *T. marneffe* has been identified using immunohistochemical techniques in tissues, and through PCR testing of a skin biopsy specimen using a set of primers specific for the fungus
- **Galactomannan antigen detection** — can show cross-reactivity with *T. marneffe*. Titers in patients with talaromycosis appear to be lower than those noted in patients with

Treatment

- Antifungal treatment should be initiated as soon as possible for patients with talaromycosis. The mortality rate has been reported to be as high as 97 percent if the infection goes untreated, or if there is a delay in diagnosis
 - Severe disease is characterized by multiple organ involvement with respiratory failure or circulatory collapse
 - Moderate disease is characterized by multiple organ involvement without respiratory failure or cardiovascular collapse
 - Mild disease refers to patients who only have skin lesions
- Patients should receive an induction course of therapy followed by long-term maintenance therapy until they have had restoration of cellular immunity
- Patients with moderate to severe disease should be treated with intravenous therapy, and then transitioned to an oral regimen. Those with mild disease can receive an oral regimen for the entire treatment duration

Talaromyces

- In this patient, treatment with intravenous amphotericin B was initiated, and 2 weeks later, antiretroviral therapy was started. Four months later, the cutaneous papules had diminished substantially, with residual superficial atrophic scars



Case 5

What is the best treatment option?

- A. Rifampin, Isoniazid, Ethambutol and Pyrazinamide (not TB)
- B. Ceftazidime (not bacterial)
- C. **Amphotericin B**
- D. Trimethoprim-Sulfamethoxazole (not PJP/PCP)

Case 6

- A forty-one year old heterosexual male with a history of HIV infection
- Previously diagnosed with HIV in 2005. He had a history of non-compliance with his highly active antiretroviral therapy (HAART) and was currently not on any medications
- complains of fever, night sweats, cough and undocumented weight loss for the past four weeks
- Laboratory studies demonstrated a WBC count of $3.73 \times 10^3/\text{mm}^3$, normal liver function profile, CD4 count of $130/\text{mm}^3$ and viral load of $>500,000$ copies/ml. PPD previously positive
- CXR revealed mild increase in interstitial markings
- HRCT is shown



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Case 6

- What is the most likely diagnosis?
 - A. PJP
 - B. Kaposi's sarcoma
 - C. Tuberculosis
 - D. Sarcoidosis

Case 6

- What is the most likely diagnosis?
 - A. PJP
 - B. Kaposi's sarcoma
 - C. Tuberculosis
 - D. Sarcoidosis

HIV and TB Co-infection

- MTB and HIV co-infection major public health burden
- According to WHO, nearly 15% of individuals diagnosed with MTB were HIV positive and a total of 360,000 deaths were attributed to MTB-HIV coinfection alone
- MTB is the most common opportunistic infection causing exacerbation of viral load and diminished CD4 count in HIV patients
- Remains the leading cause of death in patients with Acquired Immunodeficiency Syndrome (AIDS)

HIV and TB Co-infection

- Reciprocally, by decreasing the body's cell mediated immunity, HIV increases the risk of MTB progression and reactivation of LTBI
- HIV coinfection can alter the pathogenesis of MTB and lead to negative sputum smear results, atypical radiographic manifestations and extrapulmonary manifestations, which poses difficulty in diagnosing MTB disease
- The synergistic repressive effect of MTB and HIV on the immune system, drug interactions and their overlapping toxicities, and IRIS complicate the co-treatment of MTB and HIV

HIV and TB Co-infection

- Challenges include cumulative drug toxicities, potential drug interactions, pill burden and complications such as IRIS and multi-drug resistant TB
- WHO and CDC guidelines recommend the standard 6-month course of MTB therapy consisting of INH, RIF, EMB and PZA regardless of HIV status
- In HIV infected individuals with CD4 count of $<200 \text{ mm}^3$, guidelines recommend starting HAART between 2 and 8 weeks after initiation of anti-TB medications

- May develop in MTB and HIV co-infected patients who are treated with anti-TB medications concomitantly with HAART
 - 11%–45% of patients co-infected with TB and HIV, and is enhanced with early institution of therapy, as circulating CD4s cause exaggerated response to the macrophage-restricted *M. tuberculosis*
 - Predictors include CD4 count <50 cells/mm³; higher on-antiretroviral therapy (ART) CD4 counts; high pre-ART and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and less than 30-day interval between initiation of TB and HIV treatments
 - However, the strong emphasis is not to delay treatment for either illness

Case 6

- What is the most likely diagnosis?
 - A. PJP (would expect more ground glass)
 - B. Kaposi's sarcoma (usually in MSM)
 - C. Tuberculosis
 - D. Sarcoidosis (in HIV must suspect infection first)

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