

“I Can’t Stop Coughing”

A true account of an actual case

ACOI Specialty Grand Rounds

May 13, 2022

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Disclosures

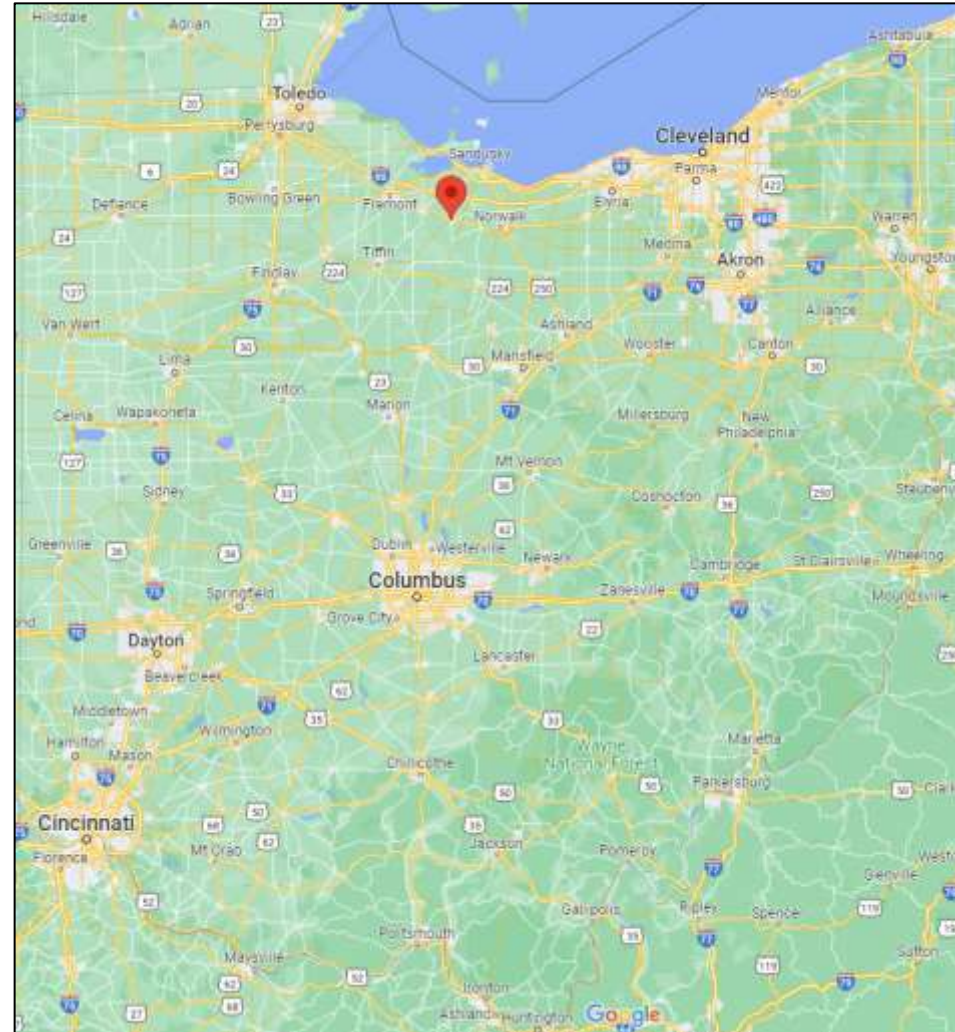
- I have no financial ties to any company

Objectives

- Review findings while progressing through the case
- Formulate a differential
- Discuss teaching points
- Create a plan of care

Bellevue, Ohio

- Bellevue, Ohio
 - 61mi SW Cleveland
 - 45mi SE Toledo
- The Bellevue Hospital
 - Independent
 - Community hospital
 - 50 acute care beds



October 24, 2021

The ER Visit

10/24/2021: ER

- 58yo male with a 5 day history of dry cough
 - Other symptoms:
 - Fever (Tmax 104°F)
 - N/V (for 1st 3 days, now resolved)
 - Body aches
 - Fatigue
 - Home COVID-19 test negative

10/24/2021: Patient History

- PMH:
 - Rheumatoid arthritis
 - History of atrial flutter
- PSH:
 - Bilateral rotator cuff repair
 - Left knee meniscal repair
- Social:
 - Tobacco: Never smoker
 - EtOH: 1-2 drinks a month
 - Illegal: Denies
 - Occupation: Farmer

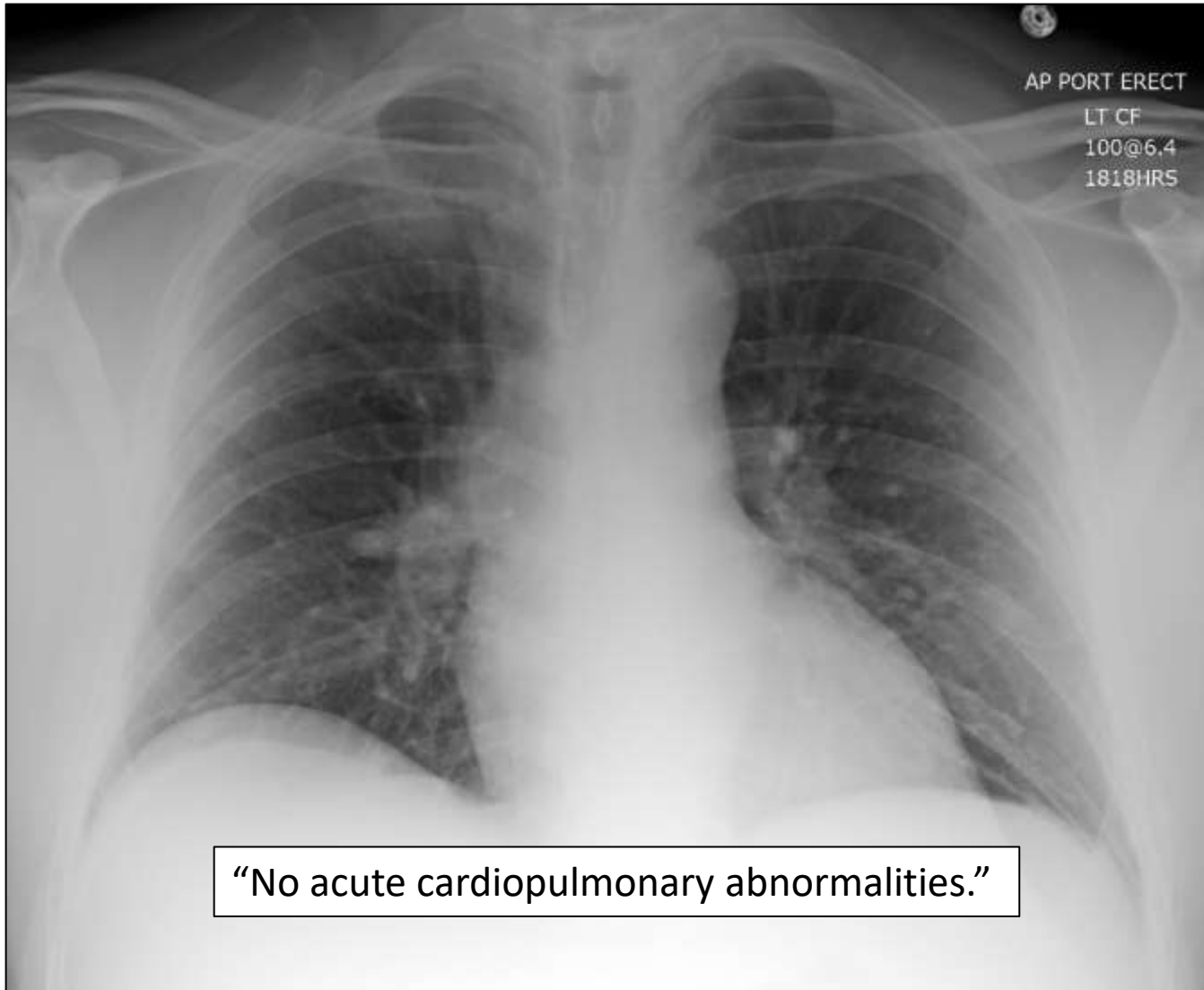
10/24/2021: Patient History cont.

- Allergies:
 - Aspirin, cefazolin (anaphylaxis)
- Home meds:
 - Apixiban
 - Diltiazem
 - Atenolol
 - Methotrexate
 - Adalimumab (Humira®)
 - Folic acid

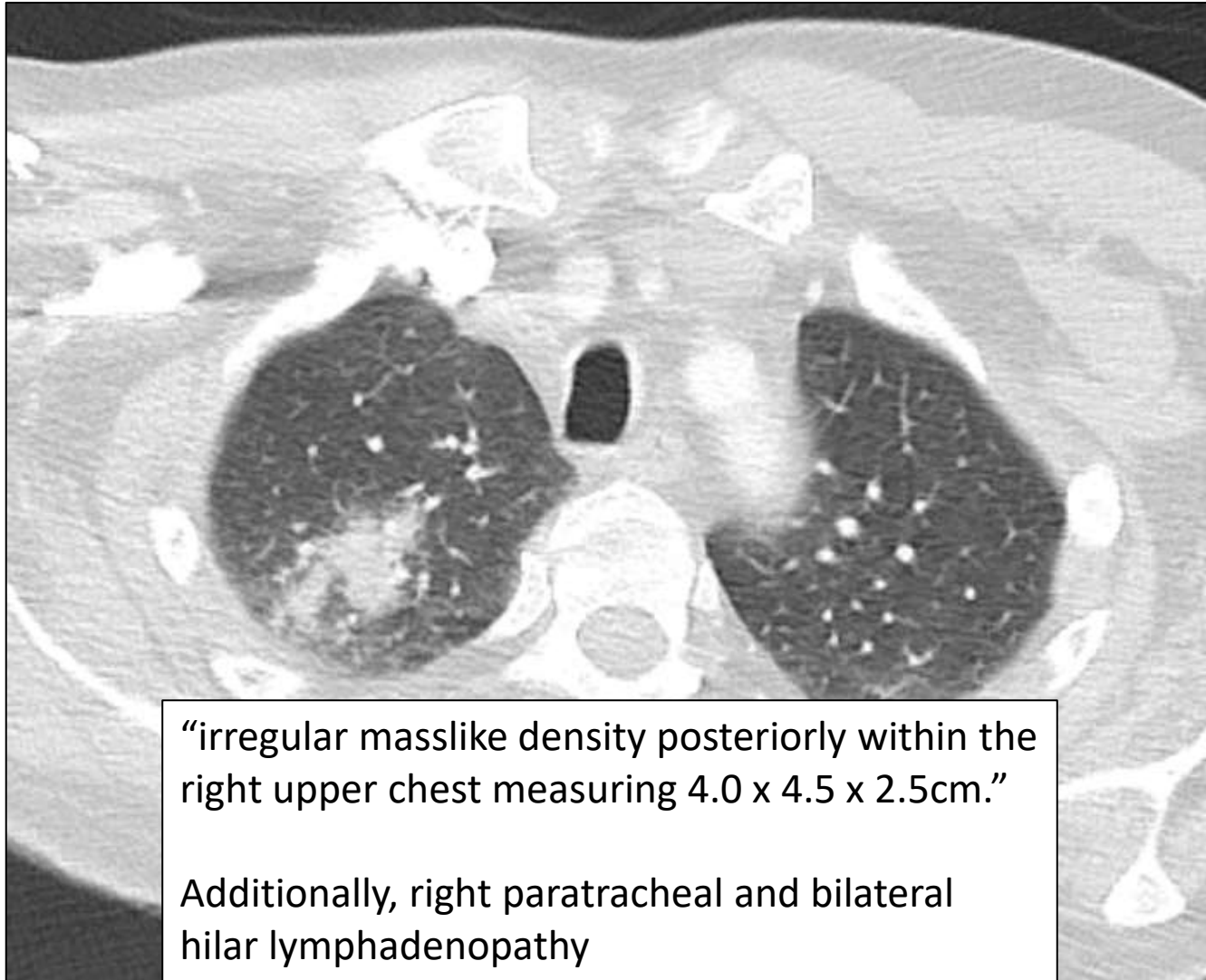
10/24/2021: Labs

- Na⁺: 134mmol/L
- K⁺: 3.8mmol/L
- Cl⁻: 99mmol/L
- HCO₃⁻: 27mmol/L
- Glu: 96mg/dL
- BUN: 18mg/dL
- Cr: 1.3mg/dL
- GFR: 57mL/min
- ALT: 398units/L Ref: 21-72
- AST: 287units/L Ref: 17-59
- Alkaline phosphatase:
265units/L Ref: 38-126
- Total bilirubin:
1.1mg/dL
- Albumin: 3.5g/dL
- WBC: 10.2
- Hb: 14.3g/dL
- Plt: 113k

10/24/2021: CXR



10/24/2021: CT Chest



10/24/2021: Thoughts

- What is the differential for the RUL infiltrate/mass:
 - Infectious
 - Pneumonia
 - Inflammatory
 - Rheumatoid, Sarcoid
 - Neoplasm
 - Primary lung, metastatic
- What is with the elevated liver function tests (LFTs)?

10/24/2021: Discharge

- ER physician noted the fever and consolidation, as well as elevated LFTs
 - Questioned pneumonia, as well as concerned it could be associated with rheumatoid arthritis \pm methotrexate and/or adalimumab
- Plan per ER:
 - Azithromycin (Z-Pak[®])
 - Steroid taper
 - Albuterol PRN
 - Copy of CT given to patient for his records, recommended repeat CT in future

Teaching Point #1

- Community acquired pneumonia

Typicals	Atypicals
Streptococcus pneumoniae	Legionella pneumophila
Moraxella catarrhalis	Mycoplasma pneumoniae
Haemophilus influenzae	Chlamydia pneumoniae

3rd generation cephalosporin
e.g. ceftriaxone
or
ampicillin/sulbactam

Respiratory
Fluoroquinolone
e.g. levofloxacin

Macrolide
e.g. azithromycin
Tetracycline
e.g. doxycycline

October 26, 2021

The Second ER Visit

10/26/2021: ER Redux

- Patient returned to the ER feeling worse
 - Slightly better yesterday, but developed worsening chills along with continued fevers (Tmax 101.2°F)
- Further history obtained
 - Last dose of adalimumab was 10/18/2021
 - Labs are monitored by rheumatologist
 - Last available labs were from 12/10/2020:
 - Cr: 1.27mg/dL
 - ALT: 34units/L
 - AST: 14units/L
 - Alkaline phosphatase: 96units/L
 - Total bilirubin: 0.4mg/dL

10/26/2021: Repeat Labs

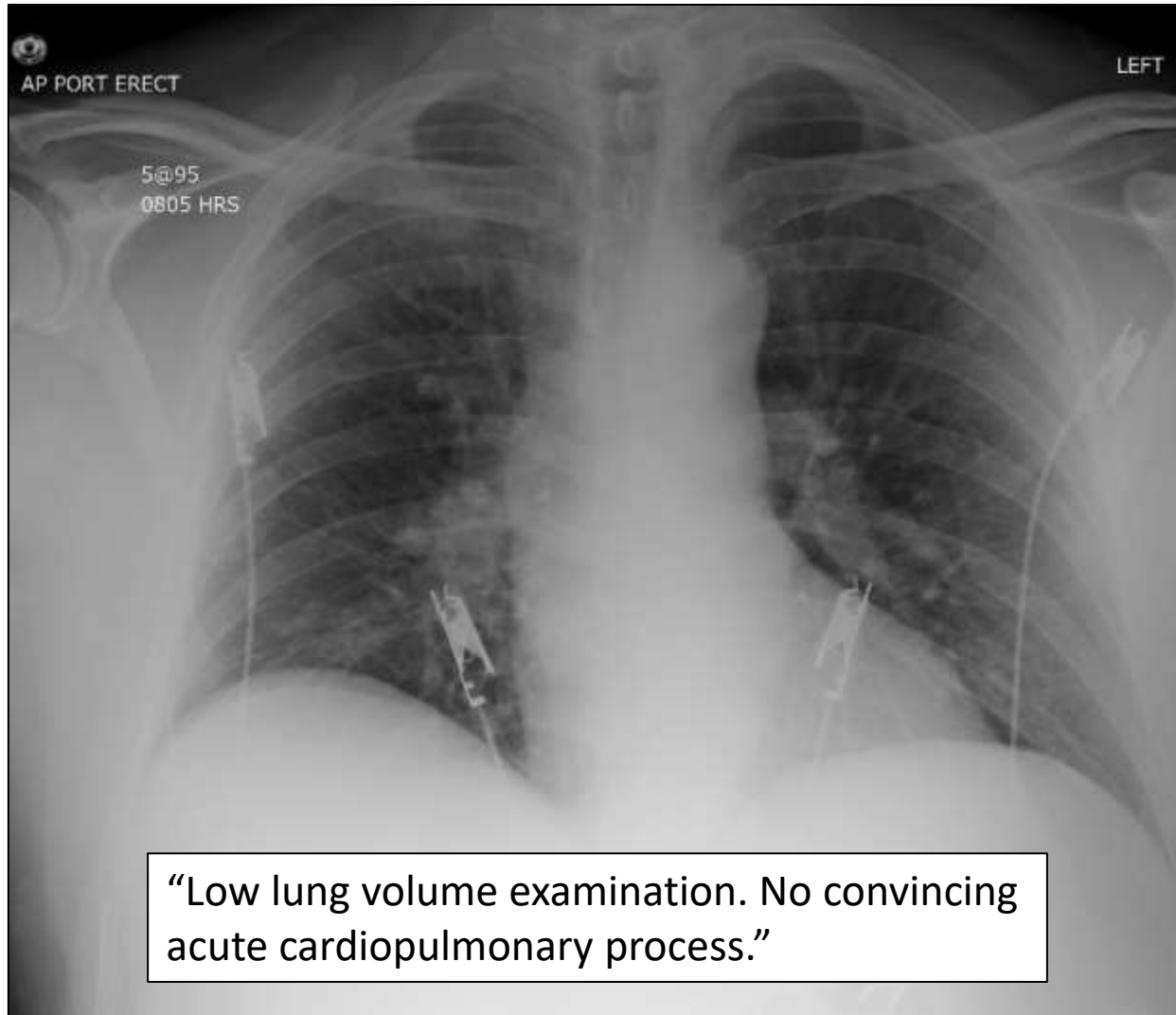
10/24/2021

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265units/L Ref: 38-126
- Total bilirubin:
1.1mg/dL
- Albumin: 3.5g/dL
- WBC: 10.2
- Plt: 113k

10/26/2021

- ALT: 684units/L
- AST: 468units/L
- Alkaline phosphatase:
263units/L
- Total bilirubin:
0.9mg/dL
- Albumin: 3.3g/dL
- WBC: 8.2
- Plt: 128k

10/26/2021: CXR



10/26/2021: Exam

- Appears stated age
- Acutely ill
 - Diaphoretic
 - Mildly dyspneic
- Crackles RUL
- Wheezes
- Mild splenomegaly

10/26/2021: Create a Problem List

- RUL infiltrate/mass
- Elevated LFTs
- Mediastinal & bilateral hilar lymphadenopathy
- Rheumatoid arthritis

10/26/2021: RUL infiltrate/mass

- Infectious

- Community acquired pneumonia
- Tuberculosis
- Opportunistic infection
- Other

- Inflammatory

- Rheumatoid arthritis
- Methotrexate
- Sarcoidosis
- Other

- Neoplasm

- Solid tumor with metastases
- Lymphoma associated with adalimumab

10/26/2021: Elevated LFTs

- Infection
 - Viral
 - Hepatitis
 - CMV (Cytomegalovirus)
 - EBV (Epstein-Barr virus)
 - Herpes
 - Other
- Autoimmune
- Drug-induced
- Wilson's disease
- Alcoholic

10/26/2021: Work Up

- ER ordered a RUQ ultrasound:
 - Abnormal gallbladder wall thickening, but no evidence convincing for cholecystitis
- Additional studies:
 - Acetaminophen level: None detected
 - Ferritin >1000
 - NH₃: 34
 - UA: Unremarkable
 - COVID-19 and influenza not detected

10/26/2021: Work Up cont.

- Pending:
 - QuantiFERON® (for TB)
 - Alpha1 Antitrypsin
 - CMV
 - Acute hepatitis panel
 - EBV
 - Ceruloplasmin
- Plan:
 - Antibiotics changed from azithromycin to levofloxacin and vancomycin
 - Patient placed in isolation until TB can be ruled out

Teaching Point #2

- Rheumatoid arthritis-associated lung nodules
 - Can be detected in at least 20% of RA patients
 - Typically multiple nodules
 - Size varies from several mm up to several cm
 - Can be mildly FDG positive on PET scan
 - Generally do not cause symptoms
 - Can cavitate, cause pneumothorax if subpleural
 - Caplan's Syndrome: RA nodules with coal mining or other inorganic dust exposure
- Accelerated nodulosis:
 - Methotrexate can increase the rate of nodule formation
 - Can occur 1 week up to 8 years after starting treatment

October 27, 2021

The Day After Admission

10/27/2021: Patient updates

- Tmax 102.4°F
- Feels better
- Still has dyspnea
- LFTs beginning to trend down
- Unsolicited opinions:
 - Several staff are providing their own interpretations of the CT report and are telling him he has cancer...
 - He is now very concerned
 - He was counseled to follow my advice and stay the course

October 28, 2021

The Third Day

10/28/2021: Patient updates

- Tmax 105.5°F
- Feels worse
- Still has dyspnea
- LFTs remain elevated

10/28/2021: Plan of care

- Bronchoscopy scheduled
 - Decision made to perform bronchoscopy with bronchoalveolar lavage to obtain cultures
 - Patient is on apixaban for history of atrial fibrillation
 - Did not want to wait 24 hours to hold apixaban to reduce bleeding risk for transbronchial biopsies
- Ibuprofen for persistent fevers/hyperpyrexia
 - Avoiding acetaminophen given elevated LFTs

10/28/2021: Is Something Missing?

- Patient just is not improving
- Is there something I am missing?
 - Patient is immunocompromised
 - Rheumatoid arthritis
 - Adalimumab & methotrexate therapy
 - Re-reviewed history
 - Farmer
 - Farms 800 acres of soybeans
 - No chickens or other birds
 - No travel
 - Does not go spelunking
 - No bat/guano exposure
- ? Fungal

Teaching Point #3

- Pulmonary fungal infections (not all exhaustive list)
 - Aspergillosis
 - *Aspergillus* spp. including *fumigatus*, *flavus*, *niger*
 - Multiple pulmonary & extrapulmonary manifestations
 - Aspergillus nodules
 - Aspergilloma
 - Allergic bronchopulmonary aspergillosis (ABPA)
 - Invasive aspergillosis
 - Blastomycosis
 - *Blastomyces* spp. endemic to North America
 - Ohio & Mississippi river basins, Great Lakes, St. Lawrence River
 - Found in decaying leaves, woods, etc.
 - Majority of case are pulmonary (70%)
 - Extrapulmonary: Verrucous skin lesions, osteomyelitis, etc.

Teaching Point #3 cont.

- Coccidioidomycosis
 - *Coccidioides* endemic to Southwestern United States
 - Can manifest with rheumatological symptoms and lymphadenopathy
 - Cause of “Valley Fever”
- Histoplasmosis
 - *Histoplasma capsulatum*
 - Found worldwide, but especially in North America
 - Especially in Midwestern states, Ohio and Mississippi River valleys
 - Can present with pneumonia, lymphadenopathy

Teaching Point #4

Drug	Aspergillosis	Blastomycosis	Coccidioido.	Histoplasmosis
Amphotericin B	+	+	+	+
Fluconazole ¹	-	~	Preferred	-
Itraconazole ¹	+	Preferred	Second-line	Preferred
Ketoconazole ¹	-	Second-line	+	-
Posaconazole ¹	+	No data	No data	+
Voriconazole ¹	Preferred	~	No data	+
Caspofungin	+	No data	No data	-

1 Azole antifungal

+ Susceptible

~ Questionable coverage, but data lacking

- No susceptibility

*Information extracted from multiple sources via Uptodate.com

Teaching Point #4 cont.

- Concerns:
 - Azole antifungals:
 - Many hepatically metabolized
 - Can increase LFTs
 - Rare cases of hepatotoxicity
 - Amphotericin B:
 - Associated with an acute reaction within 3 hours of transfusion of significant chills and high fevers
 - Nicknamed “shake and bake”
 - Can cause nephrotoxicity
 - Lipid formulations created to reduce renal toxicity
 - Can also increase LFTs

10/28/2021: Plan of care cont.

- Begin evaluation for fungal cause
 - Urinary histoplasmosis galactomanan antigen ordered
 - Serum fungal antibodies ordered
 - Start amphotericin B
 - Itraconazole not stocked
 - No liposomal formulation available not stocked
 - Continue to monitor daily LFTs and creatinine
- My clinical suspicion is for histoplasmosis

October 29, 2021

The Fourth Day

10/29/2021: Patient updates

- Bronchoscopy was performed
 - BAL obtained
 - No post-op complications
- Ibuprofen:
 - Helping to finally control fevers
 - Relieving constitutional symptoms
- LFTs:
 - Beginning to trend down
- Multiple labs still pending
 - Sent out

October 30, 2021

The Fifth Day

10/30/2021: Patient updates

- Bronchoscopy AFB smear negative
 - Patient was removed from isolation
- Fevers better controlled, but now having sweats
- Labs:
 - LFTs continue to trend down, but still elevated
 - Creatinine 1.28

October 31, 2021

The Sixth Day

10/31/2021: Patient updates

- Patient continues to have fevers and sweats
- Labs:
 - Blood cultures are negative
 - AST & ALT trending down, but alkaline phosphatase up
 - Ordering GGT to differentiate between liver and bone

November 1, 2021

The Seventh Day

11/1/2021: Patient updates

- Continues to have fevers with Tmax 100.4°F
- Subjectively, patient feels better
- Labs:
 - AST & ALT continue to trend down
 - Alkaline phosphatase continues to increase
 - GGT is elevated, confirming hepatic source
 - BAL cultures return negative
 - Creatinine not changed
 - Multiple other labs still pending
- Repeat CXR ordered

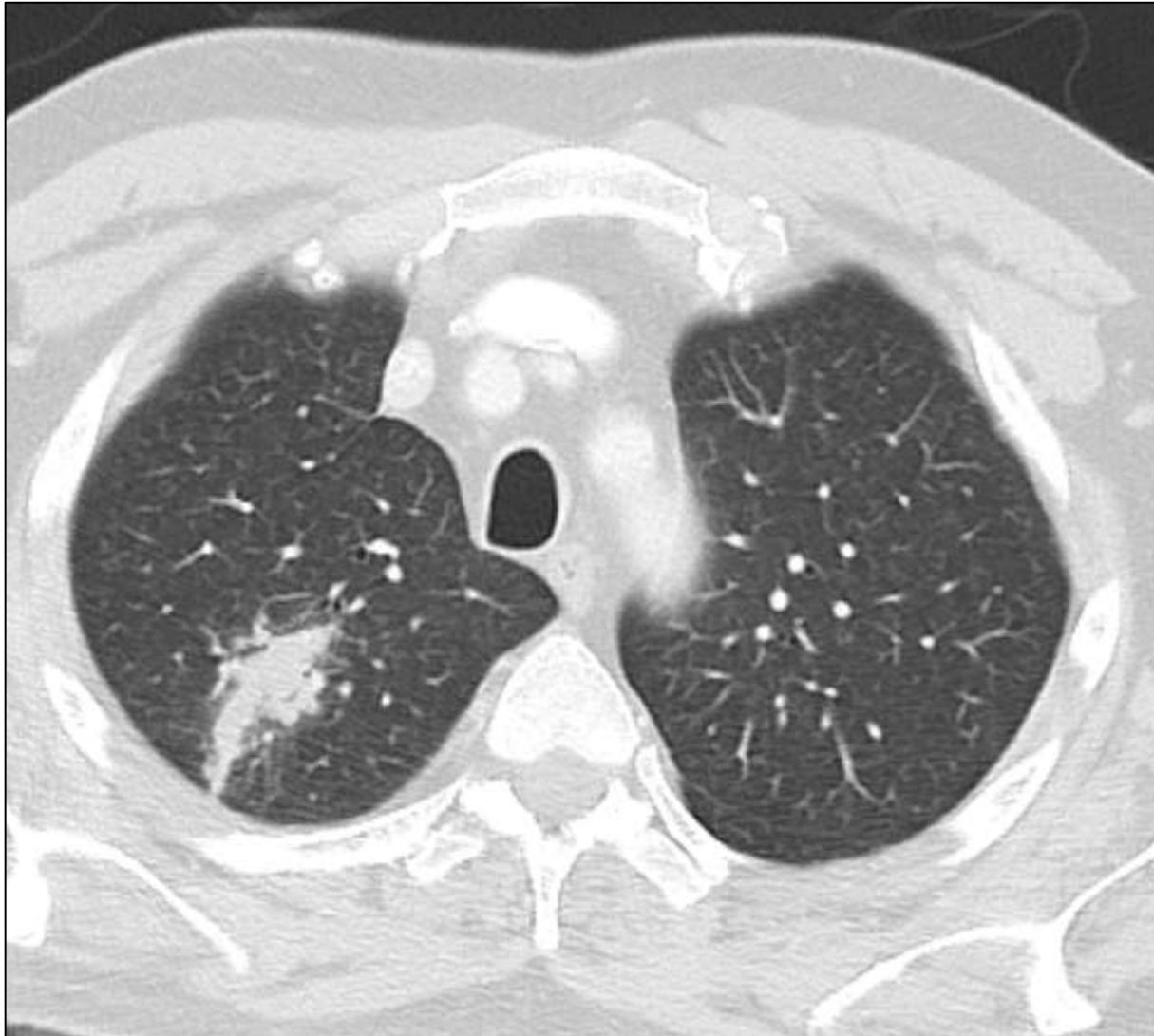
November 2, 2021

The Eighth Day

11/2/2021: Patient updates

- First day without fever
- Labs:
 - AST & ALT still trending down
 - Alkaline phosphatase is still increasing
 - CMV returns negative
- CXR shows increasing RUL density
- CT chest repeated:

11/2/2021: CT Chest



11/2/2021: Plan of care

- CT shows RUL mass:
 - Now increased in size to 4.5cm
 - More consolidated
- Still suspect fungal, especially histoplasmosis
 - Urinary antigen still pending
- Decision made to repeat bronchoscopy, this time with transbronchial biopsies under fluoroscopic guidance
 - Apixaban held for >24 hours

November 3, 2021

The Ninth Day

11/3/2021: Patient updates

- Bronchoscopy successfully completed
 - Transbronchial biopsies obtained without pneumothorax
 - No significant bleeding encountered
 - Biopsies appeared dark tan/brown (not pink as expected)
- Labs:
 - Histoplasma serum antibody elevated @ 1:32
 - Cytology from prior BAL returned negative
 - Creatinine increased now to 1.64
 - AST & ALT continue to decrease
 - Alkaline phosphatase still increasing

11/3/2021: Plan

- More certain this is histoplasmosis
 - Concerned about the increase in creatinine
 - Goal: stop amphotericin B and start itraconazole
 - Pharmacy *should* have it in by tomorrow
 - Stop scheduled ibuprofen

November 4, 2021

The Tenth Day

11/4/2021: Patient updates

- Patient states he finally feels nearly back to normal
- Labs:
 - Histoplasmosis urinary galactomannan antigen positive
 - Creatinine still elevated @ 1.75
 - LFTs, including alkaline phosphatase now trending down
 - EBV IgG *POSITIVE*
- Finally received itraconazole, patient started it without any adverse effects
- Discharged home on itraconazole

Teaching Point #5

- EBV: Signs of infectious mononucleosis
 - Malaise
 - Fever (moderate to high)
 - Tonsillitis/pharyngitis
 - Splenomegaly (50%)
 - Rash
 - Mild hepatitis (90%)
 - Lymphadenopathy
 - Cervical (posterior chain)
 - CBC changes:
 - Thrombocytopenia, atypical lymphocytes

Teaching Point #5 cont.

- Prognosis:
 - Generally good, with symptoms typically lasting 1-2 weeks
- Treatment:
 - Mainly supportive
- Long-term complications:
 - Burkitt lymphoma
 - Hodgkin lymphoma
 - Other cancers

Thoughts at discharge

- The patient had concomitant EBV?!!?!!?!!?!!?!!?!!?!!?
- Patient did not have rash, pharyngitis, or cervical lymph node enlargement
- Patient's findings suggesting EBV:
 - Elevated LFTs
 - Thrombocytopenia
 - Mediastinal/hilar lymphadenopathy
 - Splenomegaly

February 11, 2022

The Three Month Follow-Up

2/11/2022: Patient updates

- Patient has completed 12 weeks of itraconazole
 - LFTs and renal function were monitored and resolved to baseline findings
- States he feels great without any complications
- No further splenomegaly on exam
- Pathology from bronchoscopy negative for neoplasm
- CT chest was repeated:
 - Size decrease
 - Lymphadenopathy resolved
- Patient elected not to restart any biologic for RA

2/11/2022: CT Chest



Final Diagnosis

- Histoplasmosis capsulatum pulmonary infection
- Epstein-Barr virus