Pulmonary Toxicity of (Lung) Cancer Therapies

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Disclosure Statement

I **will** discuss off label use and/or investigational use of the following drugs/devices:

Prednisone

The following relevant financial relationships exist related to my role in this session:

No relationships to disclosure


I'M HAVING TROUBLE BREATHING
LYNCH
CARTOONSTOCK .com
Search ID: mlyn1148

Outline: Treatment Related Pulmonary Toxicity

- **Potential Etiologies / Patterns**
  1. **Chemotherapy** (docetaxel, gemcitabine, bleomycin)
  2. **Targeted therapy** (EGFR inhibitors, mTOR inhibitors, PD-1 and PD-L1 inhibitors)
  3. **Radiation therapy**
- **Diagnosis / Grade of Pneumonitis**
- **Management**

The importance of this challenge

- Many new therapies being developed / approved
- We must be aware of these therapies and understand their mode of action
- Important to learn to recognize, diagnose and effectively manage their toxicities

Case 1:

Special Thanks to UCSF Clinical Fellow
Alyssa Perez

Case 1

- 75 M with a history of A-fib s/p ablation, HTN, and metastatic prostate CA on treatment with docetaxel who presents with hypoxemic respiratory failure requiring high flow nasal cannula

Case 1

- Onset of SOB 10 days prior
- Rapidly progressed
- On day of presentation, EMS was called after home O2 sat in the 60s
- In ED, hypoxemic and tachypneic in the 30s, placed on HFNC FiO2 100%, 40LPM

Case 1

PMHx / PSHx:

1. Metastatic Prostate CA: dx 2006, metastatic in 2013, s/p XRT, anti-hormone agents, pembrolizumab x 2 (last 1/2017), and now on docetaxel
2. HTN
3. A-fib s/p cardioversion,
4. Appendectomy in 2011
5. Laminectomy with fusion in 2013 for metastatases

Family History: father with prostate CA

Social History: never smoker, 1 glass wine nightly, no illicits, no exposures

Home Meds:

1. cholecalciferol
2. omega-3 fish oil
3. Dexamethasone

Allergies: none

Case 1

EXAM:

Vitals: T: 37.2 HR: 115 BP: 80/60 RR: 30 O2 Sat: 91% (on 100% FiO2)

General: increased work of breathing

CV: irregularly, irregular, tachycardic, S1, S2, no murmurs

Resp: bilateral crackles diffusely

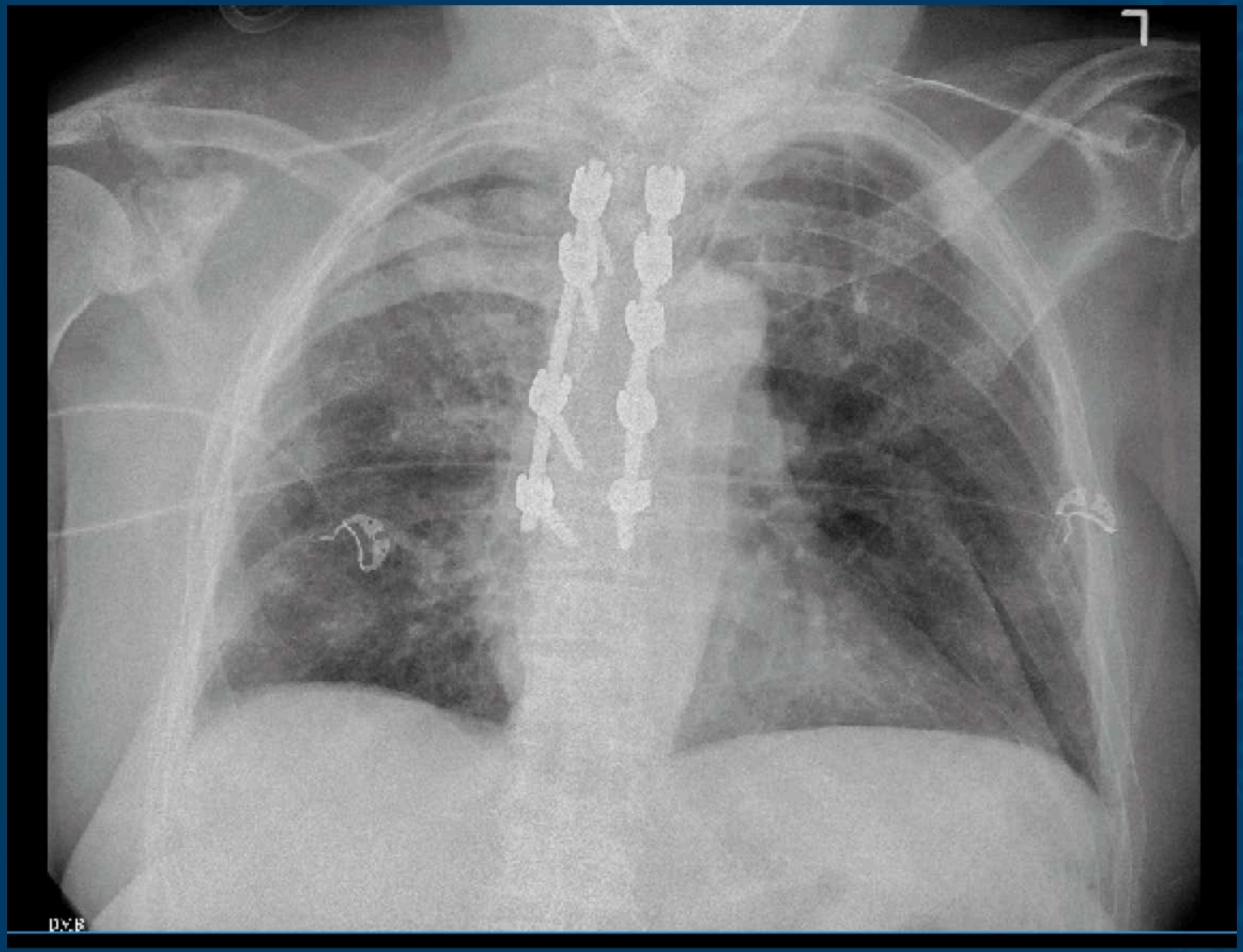
Ext: 2+ pitting edema to the mid shin b/l, +DP and TP pulses

Case 1

LABS:

BUN	41
Creat	1.13
WBC	4.4
Hgb	7.6
Trop	< 0.04
BNP	484
LDH	382

Admission CXR



Case 1: Hospital course

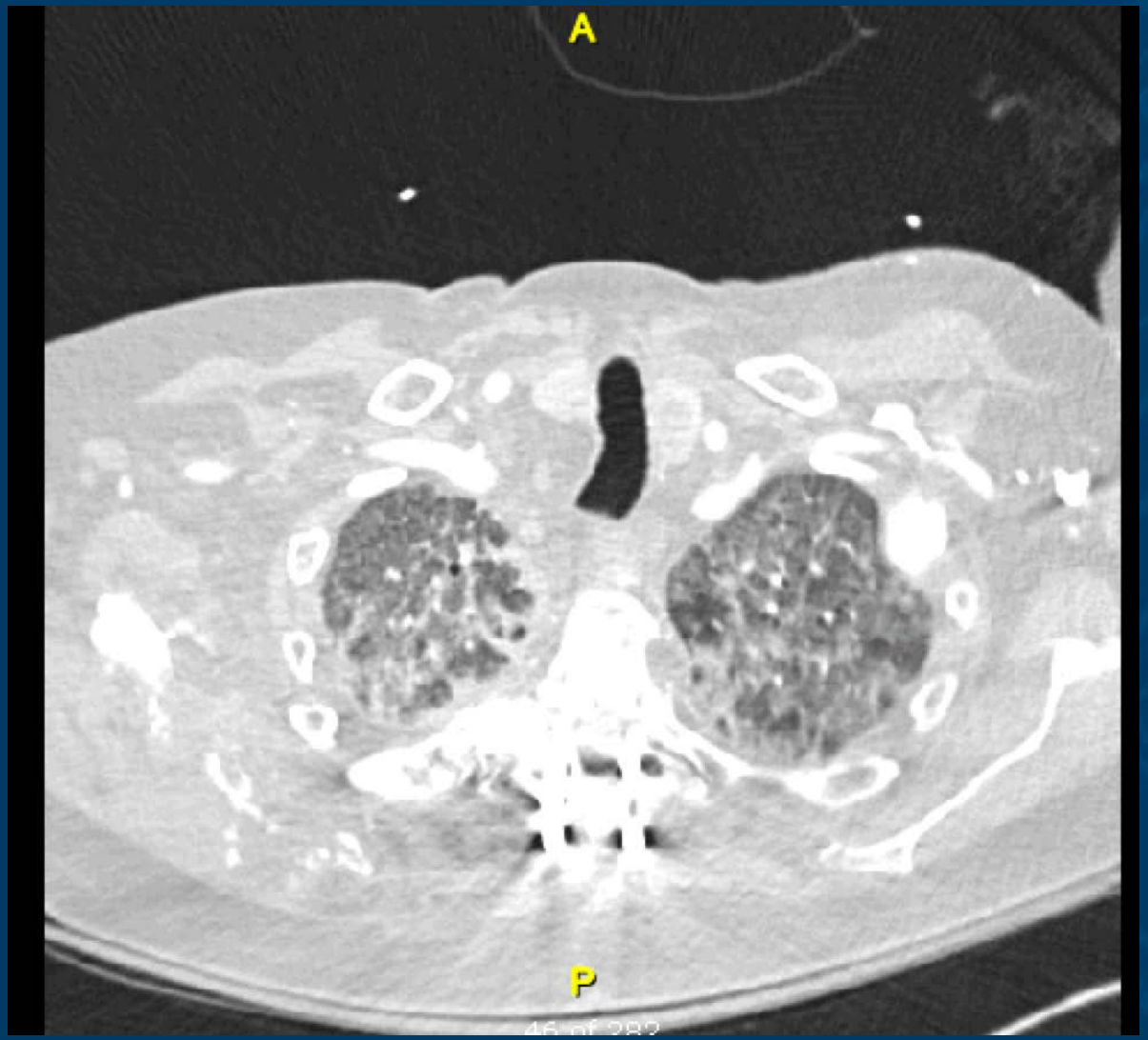
Day 1:

- Started on vancomycin and ertapenem
- Boluses of normal saline → BPs normalized.
- Pan cultured (blood, urine, sputum) & Resp viral panel sent
- Diuresed with lasix

Case 1: Hospital course

Day 2:

- TTE normal (EF 60%)
- Antibiotics broadened to include pseudomonal and atypical coverage. Diuresis continued.
- Micro: cultures remain NGTD, including Resp viral panel
- Remains afebrile, normotensive. **Continues on HFNC with FiO2 100% on 40L, sats in low 90s**
- CT scan obtained.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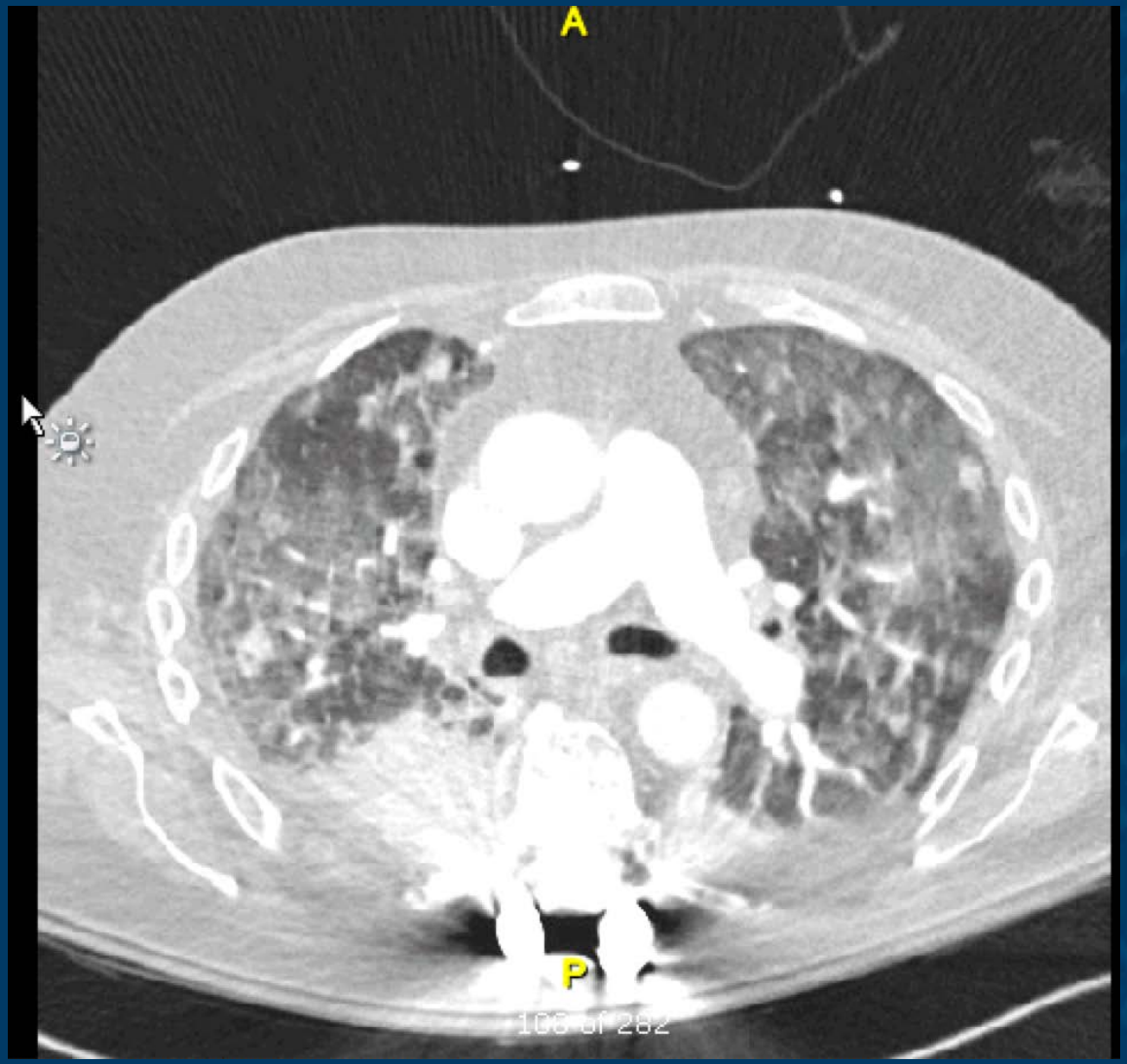
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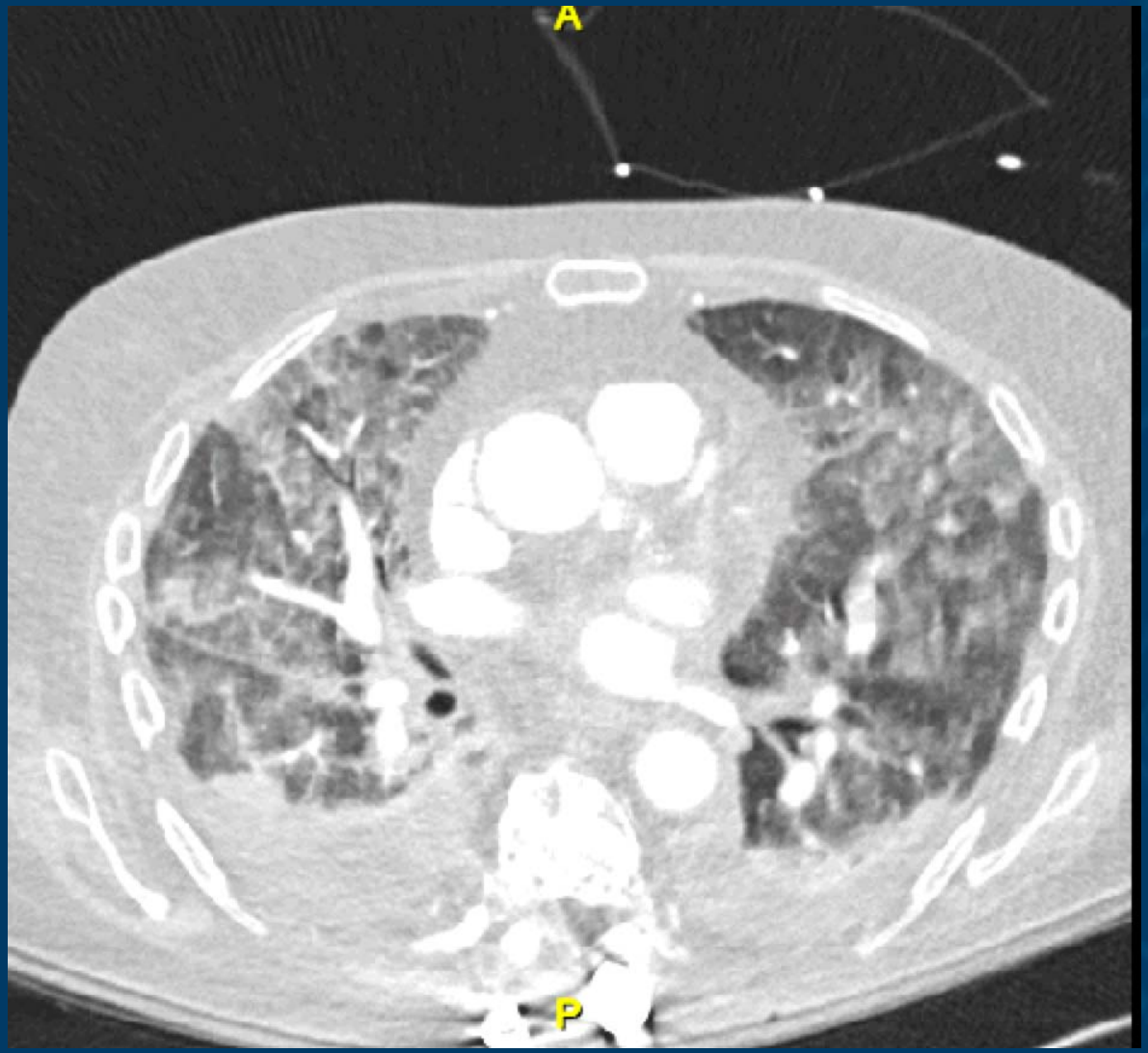
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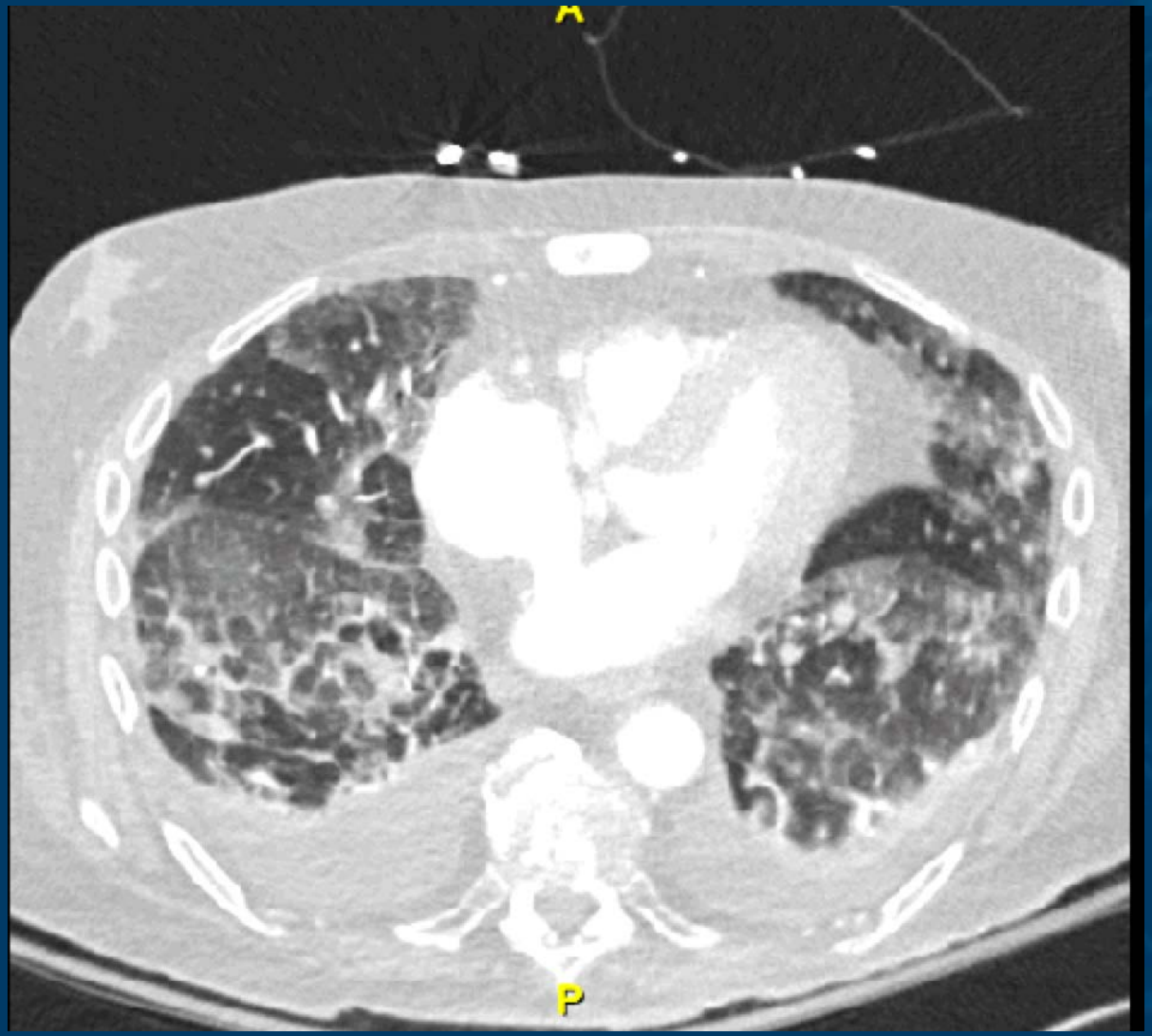
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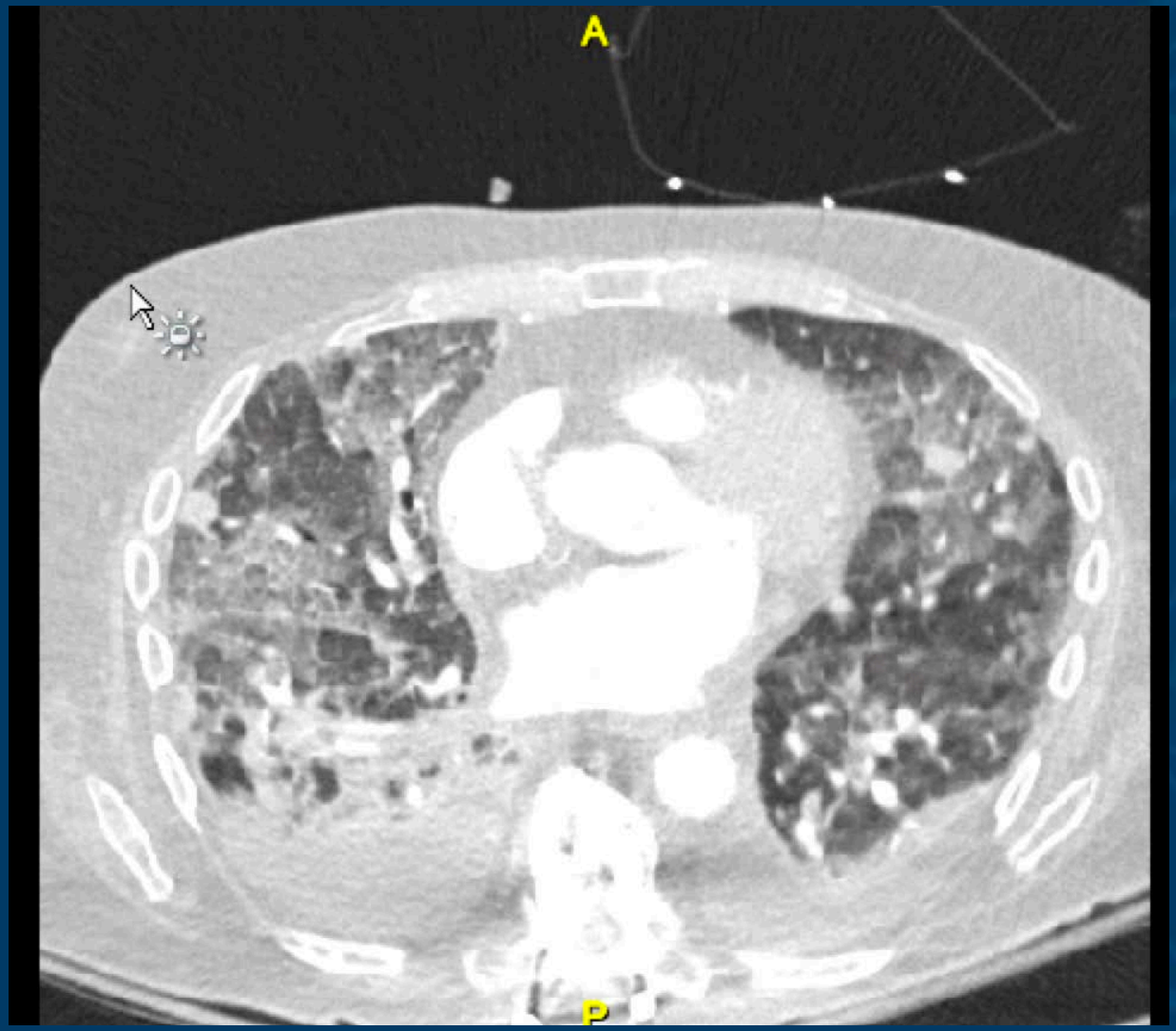
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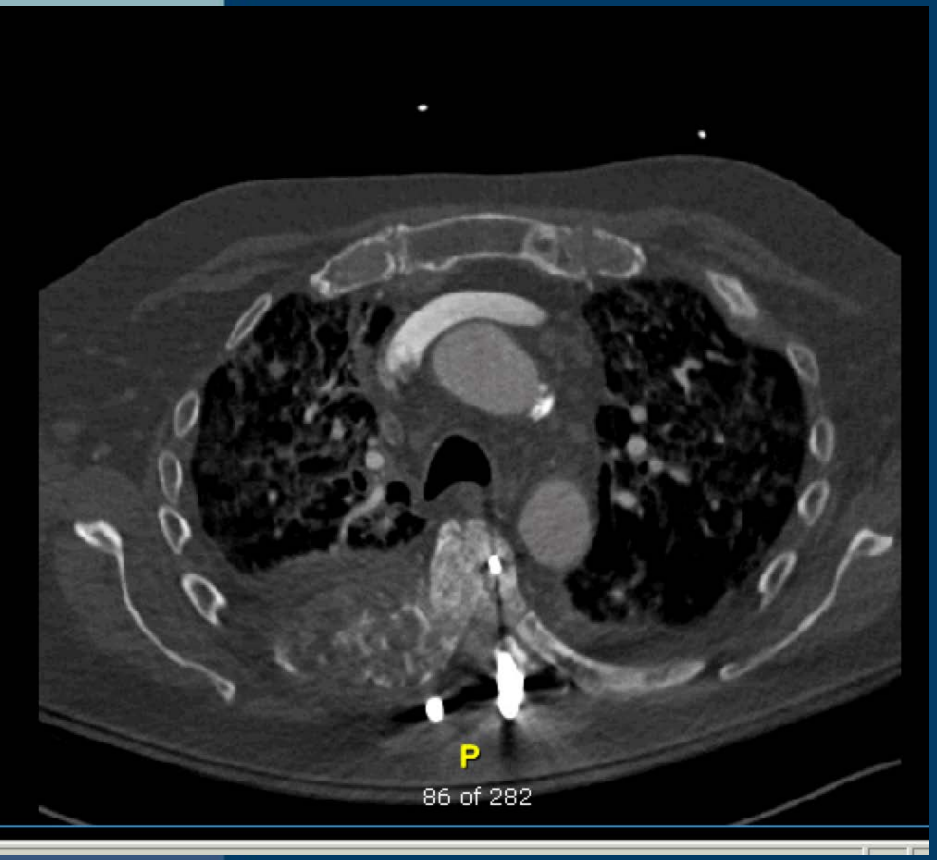
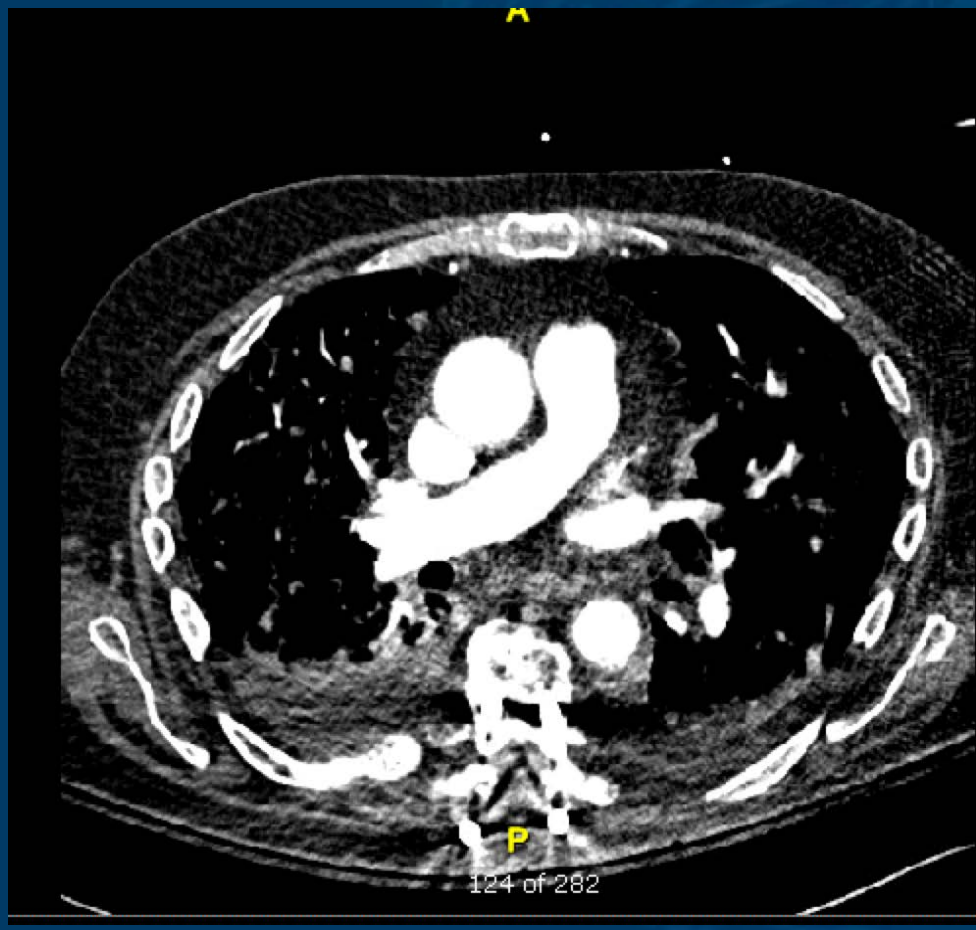


Bone Window

Soft Tissue Window



Case 1

Differential diagnosis?

Case 1: Hospital course

- **Pulmonary Consulted.**

- *Questions*
  - **What is the diagnosis?**
  - **Could this be Drug (Docetaxel) induced pneumonitis?**
  - **Should we give steroids?**

Diagnostic algorithm of pneumonitis

History/Clinical examination

- Lung co-mobidities
- Type and dose of agent
- Symptoms (Cough, Fever, Dyspnoea, Hypoxia)

Omarini, C., Thanopoulou, E. & Johnston, S.R.D. Breast Cancer Res Treat (2014) 146: 245. https://doi.org/10.1007/s10549-014-3016-5

Drug induced Lung Injury

- Unknown prevalence, thought to be under recognized globally
- Can be acute, sub-acute, or chronic
- Pathogenesis:
  - Direct damage to pneumocytes
  - Capillary leak syndrome
  - Acute or delayed hypersensitivity reaction

1. *Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. Matsuno O. Respir Res. 2012;13:39*
2. *Schwarz, Marvin; King, Talmadge. Interstitial Lung Disease, 5th Edition. 2011 637-680.*

Pre-disposing characteristics

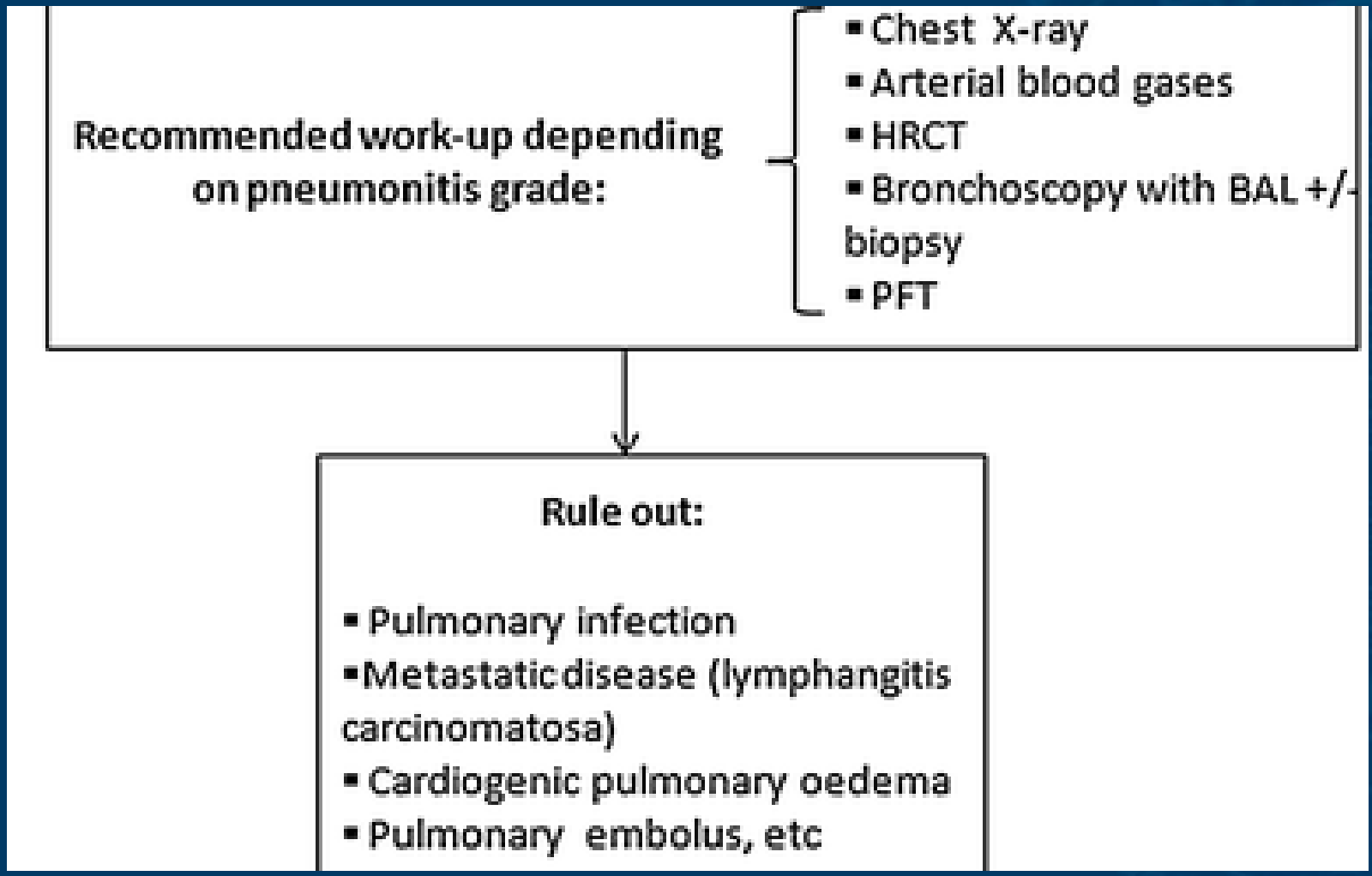
- Receiving prior chemotherapy
- Autoimmune diseases (RA, IBD),
- Extremes of age
- Prior radiation
- Pre-existing lung disease
- Smoking history

Histologic patterns

- NSIP
- OP
- Interstitial granulomas
- UIP
- DAH +/- capillaritis
- DAD
- PVOD
- DIP
- LIP
- PAP
- Eosinophilic pneumonia

Pharmacological Threat to Lungs: A Case Series and Literature Review. Irfan O, Gilani JA, Irshad A, et al. Cereus. 2017 May; 9(5): e1232

Diagnostic algorithm of pneumonitis



Omarini, C., Thanopoulou, E. & Johnston, S.R.D. Breast Cancer Res Treat (2014) 146: 245. https://doi.org/10.1007/s10549-014-3016-5

Evaluation of patient with possible Drug Induced Lung Injury

Steps	Comments
PFTs	• Lung volumes and DLCO (for baseline and monitoring)
Chest CT scan	• Exclude other possible diagnoses (tumor progression, pleural effusion, PE) • Assess pattern / monitor for change
Bronchoscopy	• BAL may be useful to rule out infection (particularly in fever / infection suspected) or to assess the lung inflammation profile • TBBx may help to obtain histology, assess for lymphangitic disease
Diagnostic tests to exclude opportunistic infections	• Bacterial pneumonia (typical acute lobar pneumonia) • Viral pneumonia (Respiratory Viral PCR) • Other bacterial infections (including *Legionella* infection, particularly in hospitalized patients) • Invasive fungal infections (e.g., *Pneumocystis jiroveci*, *Pneumocystis carinii* infection, Aspergillosis)
Consider other causes	• Pulmonary edema / Heart failure

Back to Case 1…

Day 2 continued:

- All micro data NGTD including blood, sputum, urine, and RVP
- Not improving despite diuresis and Echo did not suggest heart failure
- Bronchoscopy considered but deferred given oxygen requirement and DNR/DNI status

Drug induced Lung Injury

Chemotherapeutic Agents
• Bleomycin
• Bortezomib
• Busulfan
• Carmustine
• Chlorambucil
• Colony-stimulating factors
• Cyclophosphamide
• Cytarabine
• Deferoxamine
• Docetaxel
• Doxorubicin
• Erlotinib
• Etoposide
• Fludarabine

Radiologic and Pathologic Findings with Docetaxel Induced Lung Injury:

-Acute ILD
-Subacute ILD
-Transient Infiltrates
-Pulmonary Edema
-ARDS
-DAH
-DAD

Schwarz, Marvin; King, Talmadge. Interstitial Lung Disease, 5th Edition. 2011 637-680.

Matsuno O. Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. Respir Res. 2012;13:39

Docetaxel induced pneumonitis

Docetaxel = taxane used to treat solid tumors

Proposed Mechanisms of Injury:

- **Acute: Type 1 Hypersensitivity reaction**
  - Dyspnea, bronchospasm, hypotension
  - Incidence is 30% of patients; decreases to 1-3% of patients with steroid pre-medication
- **Acute-Subacute: Type IV Hypersensitivity reaction**
  - Few hours to 2 weeks
  - Characterized by bilateral pulmonary opacities

Grande, C; Villanueva, MJ; Huidobro, G, et al. Docetaxel-induced interstitial pneumonitis following non-small cell lung cancer treatment. Clin Transl Oncol (2007) 9:578-581.

Docetaxel induced pneumonitis

Acute-Subacute: Type IV Hypersensitivity reaction

- Presents as insidious onset
- Symptoms: dyspnea, malaise, chest pain, cough, and fever
- Also associated with edematous state: edema and pleural effusions
- Imaging generally shows bilateral pulmonary infiltrates
  - Most common pattern = NSIP, DAD, pleural effusions

1. *Charpidou, AG; Gkiozos, I; Tsimpoukis, S, et al. Therapy-induced Toxicity of the Lungs: An Overview. Anticancer Research Feb 2009 vol. no. 2 631-639.*
2. *Grande, C; Villanueva, MJ; Huidobro, G, et al. Docetaxel-induced interstitial pneumonitis following non-small cell lung cancer treatment. Clin Transl Oncol (2007) 9:578-581.*

Docetaxel induced pneumonitis

- Factors that increase likelihood of developing severe pneumonitis:
  - Schedule > Dose
  - Combination therapy with gemcitabine
  - Radiation treatment
- A 2012 retrospective study found increased incidence of pneumonitis in patients with NSCLC treated with docetaxel who had baseline pulmonary dysfunction
  - 25.9% vs 4.6% general incidence
  - Recommended *against* the use of docetaxel in patients with pre-existing lung disease

1. *Charpidou, AG; Gkiozos, I; Tsimpoukis, S, et al. Therapy-induced Toxicity of the Lungs: An Overview. Anticancer Research Feb 2009 vol. no. 2 631-639.*
2. *Grande, C; Villanueva, MJ; Huidobro, G, et al. Docetaxel-induced interstitial pneumonitis following non-small cell lung cancer treatment. Clin Transl Oncol (2007) 9:578-581.*

Docetaxel induced pneumonitis

- Thought to be a a steroid responsive process but case reports range from steroid responsive pneumonitis to steroid unresponsive pneumonitis to development of fibrosis
- General recommendation is prompt treatment with steroids
  - No consensus on dose

1. *Pankowska-Supryn, M; Zaleska, Ml Roszowska-Sliz, B, et al. Interstitial lung disease associated with docetaxel in a patient treated for breast cancer – a case report. Pneumonol Alergol Pol 2015; 83: 378-382*
2. *Genestreti, G; Battista, M; Trisolini, R. A Commentary on interstitial pneumonitis induced by docetaxel: clinical cases and systematic review of the literature. Tumori Journal. Vol. 100 Issue 3, May-Jun 2015, pp249-346*
3. *Tamiya, A; Naito, T; Miura, S, et al. Interstitial Lung Disease Associated with Docetaxel in Patients with Advanced Non-small cell Lung Cancer. Antcancer Research 32: 1103-1106 (2012).*
4. *Ochoa, R; Bejarano PA; Gluck, S, et al. Pneumonitis and pulmonary fibrosis in a patient receiving adjuvant docetaxel and cyclophosphamide for stage 3 breast CA: a case report and literature review.*

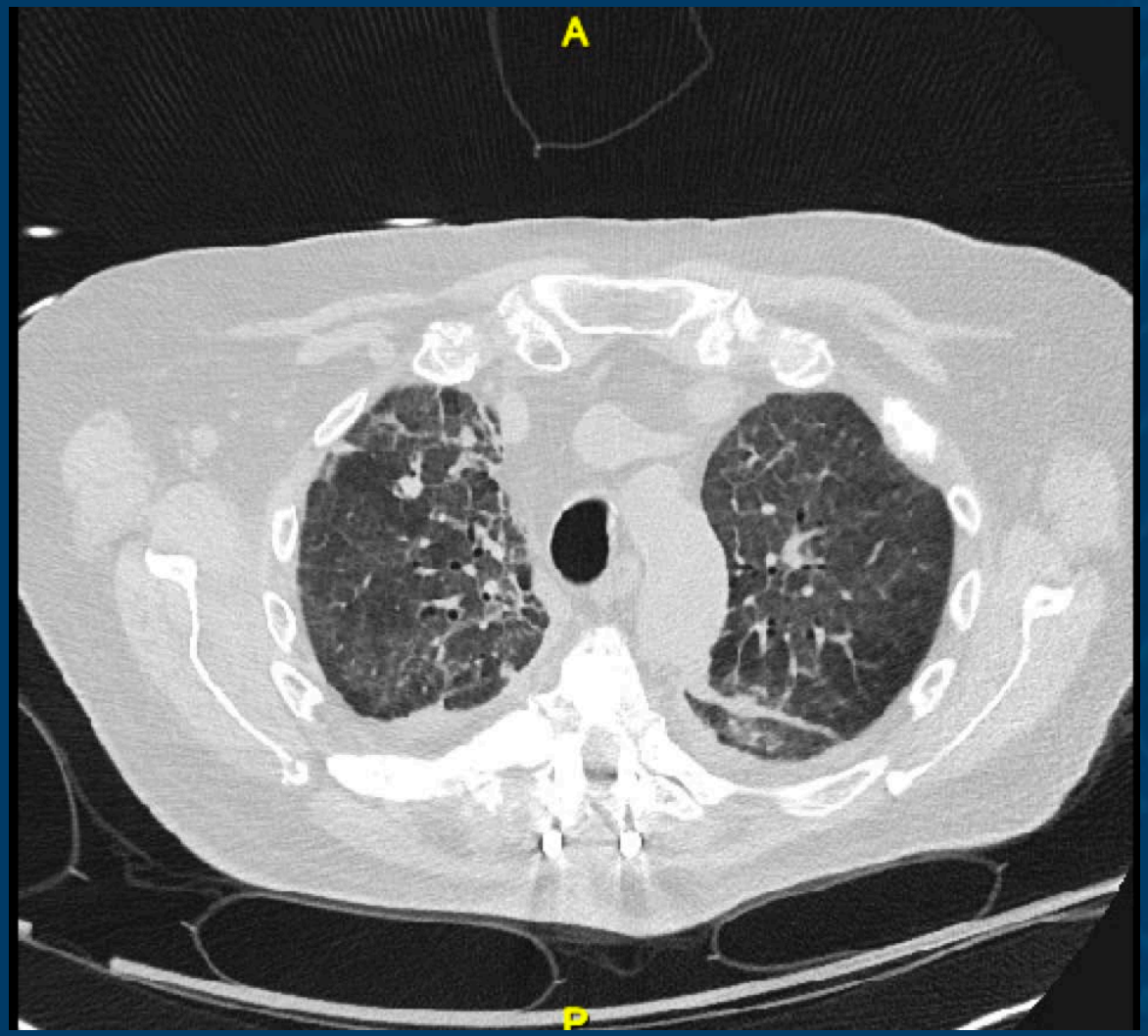
Case 1: Hospital course

Day 3:

- Started on methylprednisolone 125 mg IV Q6 hours
- Patient subjectively feels improved

Day 4:

- Improvement in oxygen requirement to 50% FiO2 40L HFNC
- Patient continues to feel better, no longer tachypneic at rest
- Chest CT repeated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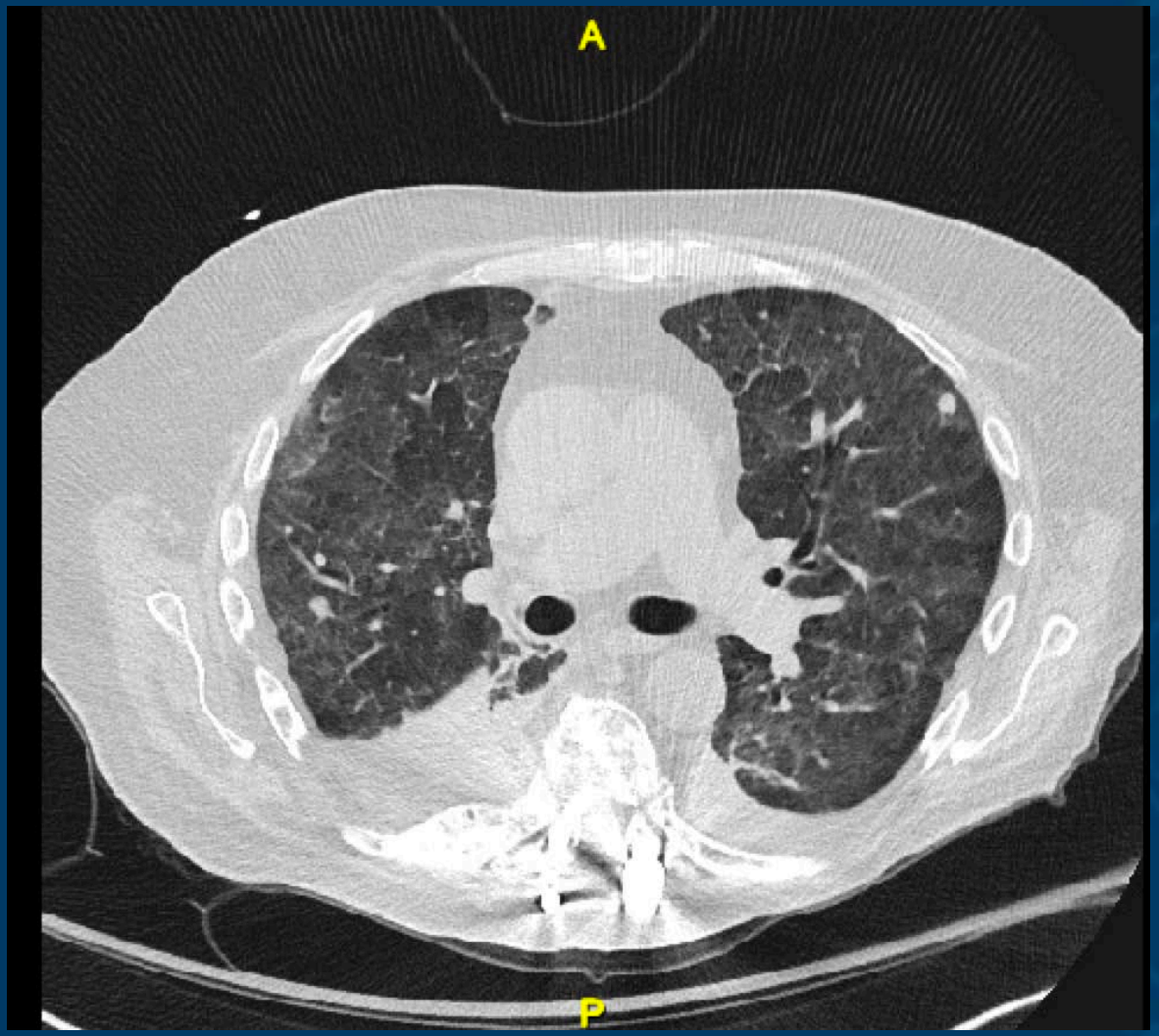
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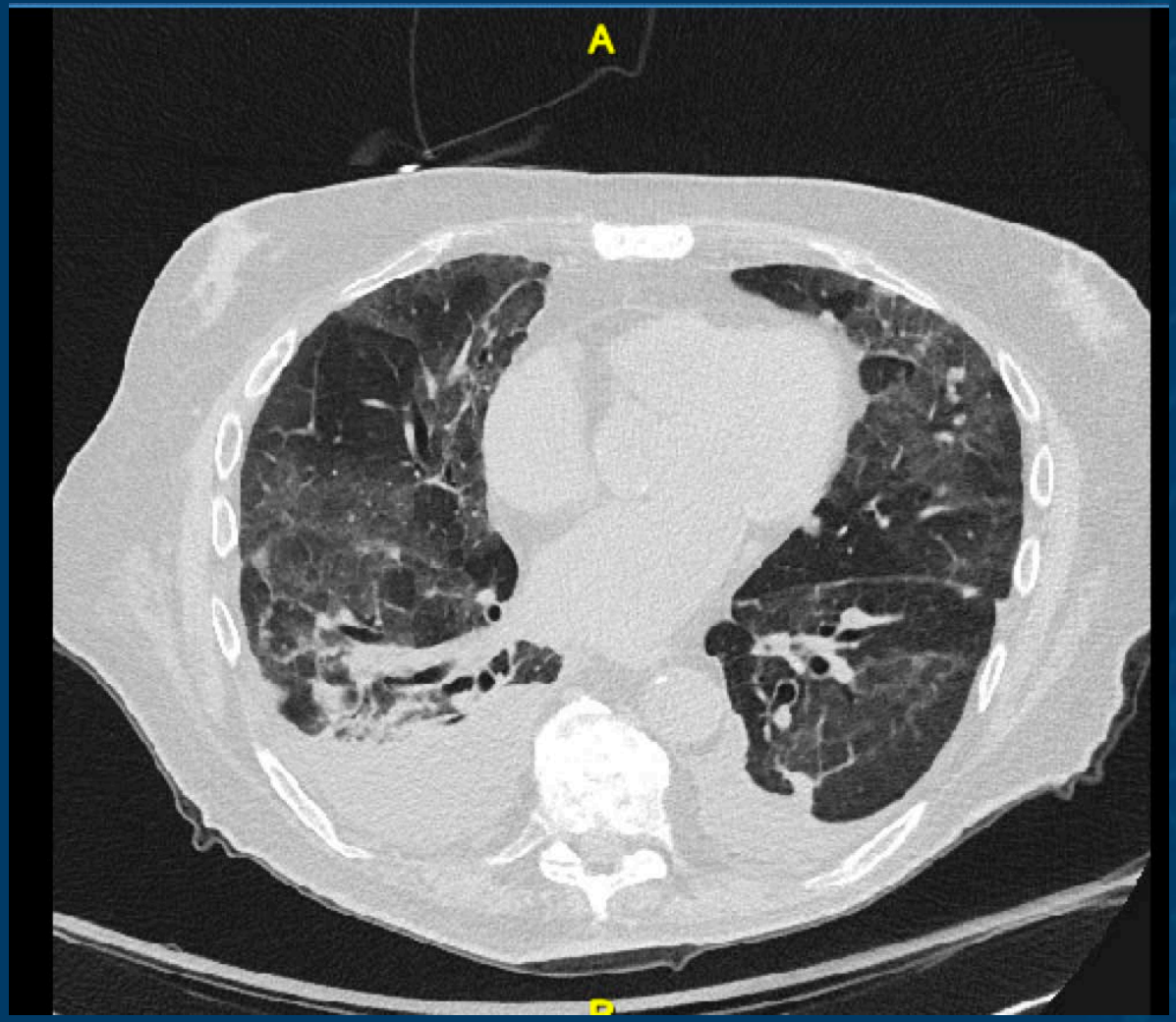
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Case 1: Hospital course

Day 5:

- Ongoing improvement, down to 6L NC
- Steroids changed to prednisone 40 mg PO daily

Day 6:

- Discharged home
- Plan for slow taper of prednisone

Take away points

- Need to consider drug induced lung injury in patients on chemotherapy
- Docetaxel is a rare but well-associated cause of pneumonitis, most commonly presenting with subacute dyspnea and bilateral ground glass opacities
  - Treatment is prompt initiation of steroids, 0.5-0.7 mg/kg prednisone likely sufficient
- Consider avoiding docetaxel in patients with pre-existing lung disease

Case 2:

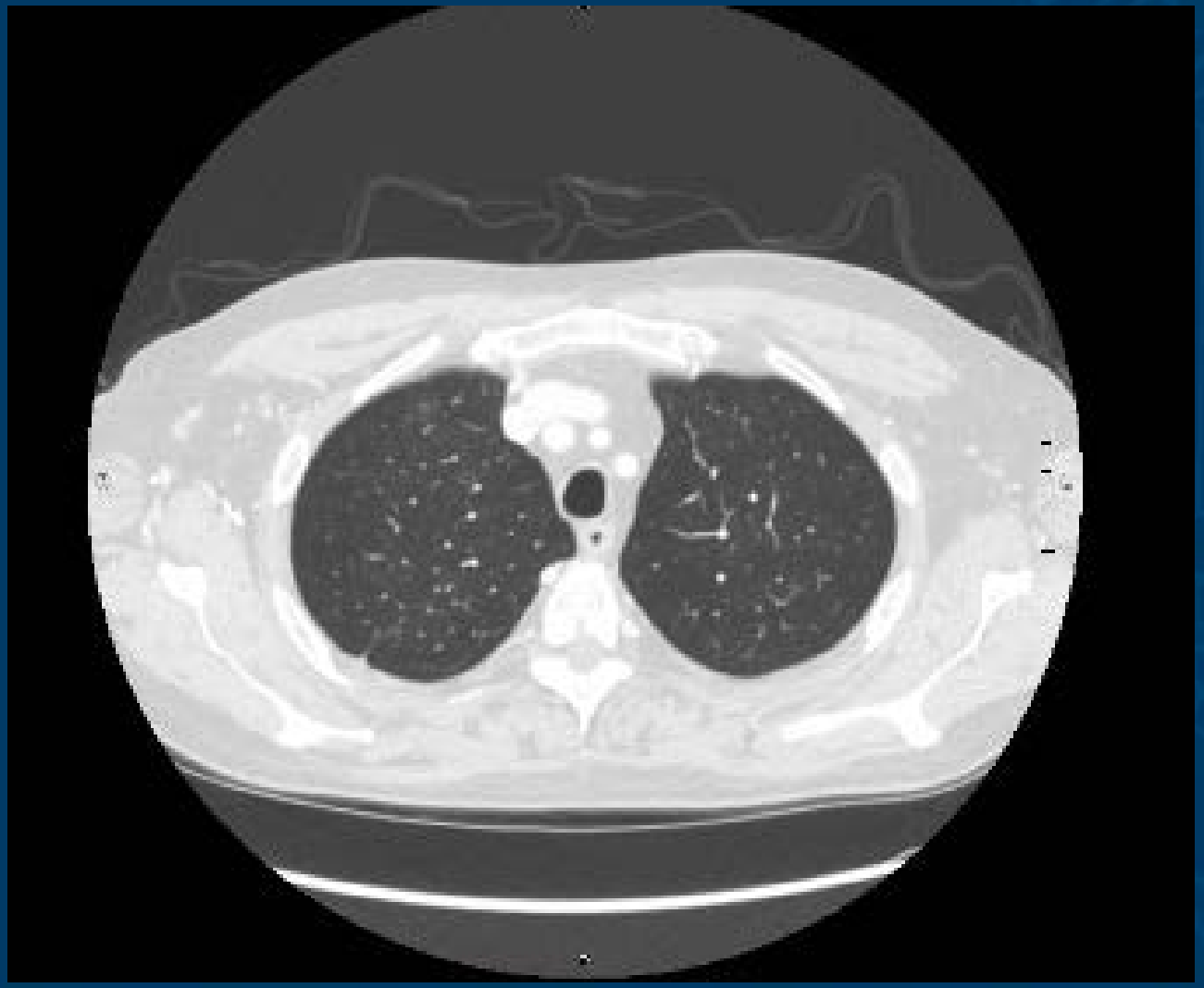
Case 2

- **67 y.o. man** with metastatic Prostate Cancer (bone, testes, brain). Initally diagnosed in 2005, s/p multiple treatments. Referred to pulmonary for complaints of dyspnea on exertion, dry cough x 3 weeks and an abnormal chest CT scan.
- SpO2 at rest 96% on RA

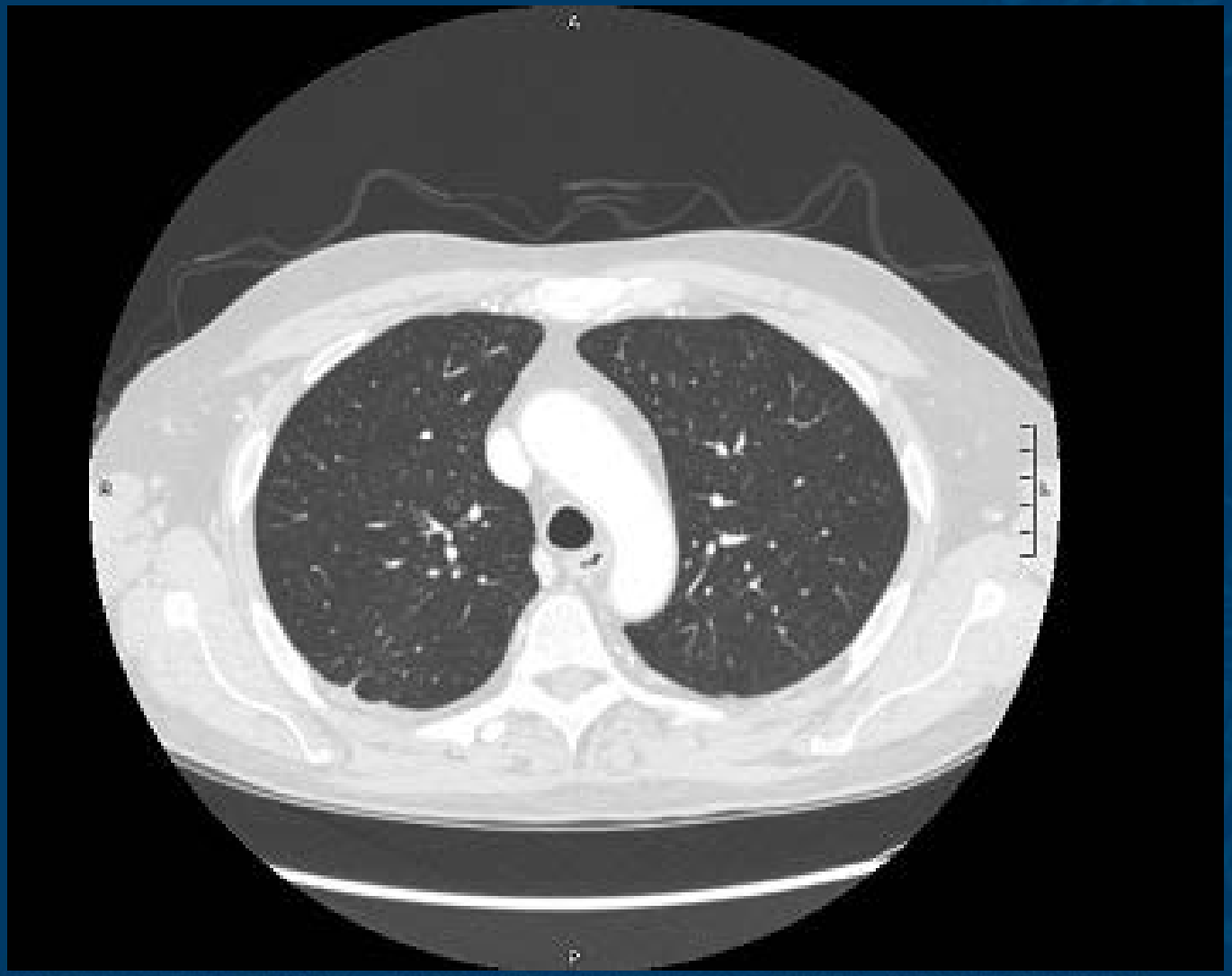
Case 2 – What is your differential diagnosis?

- Metastases to lung
- Pulmonary emboli
- Infections
- Pulmonary edema
- Pneumonitis due to drugs or RT

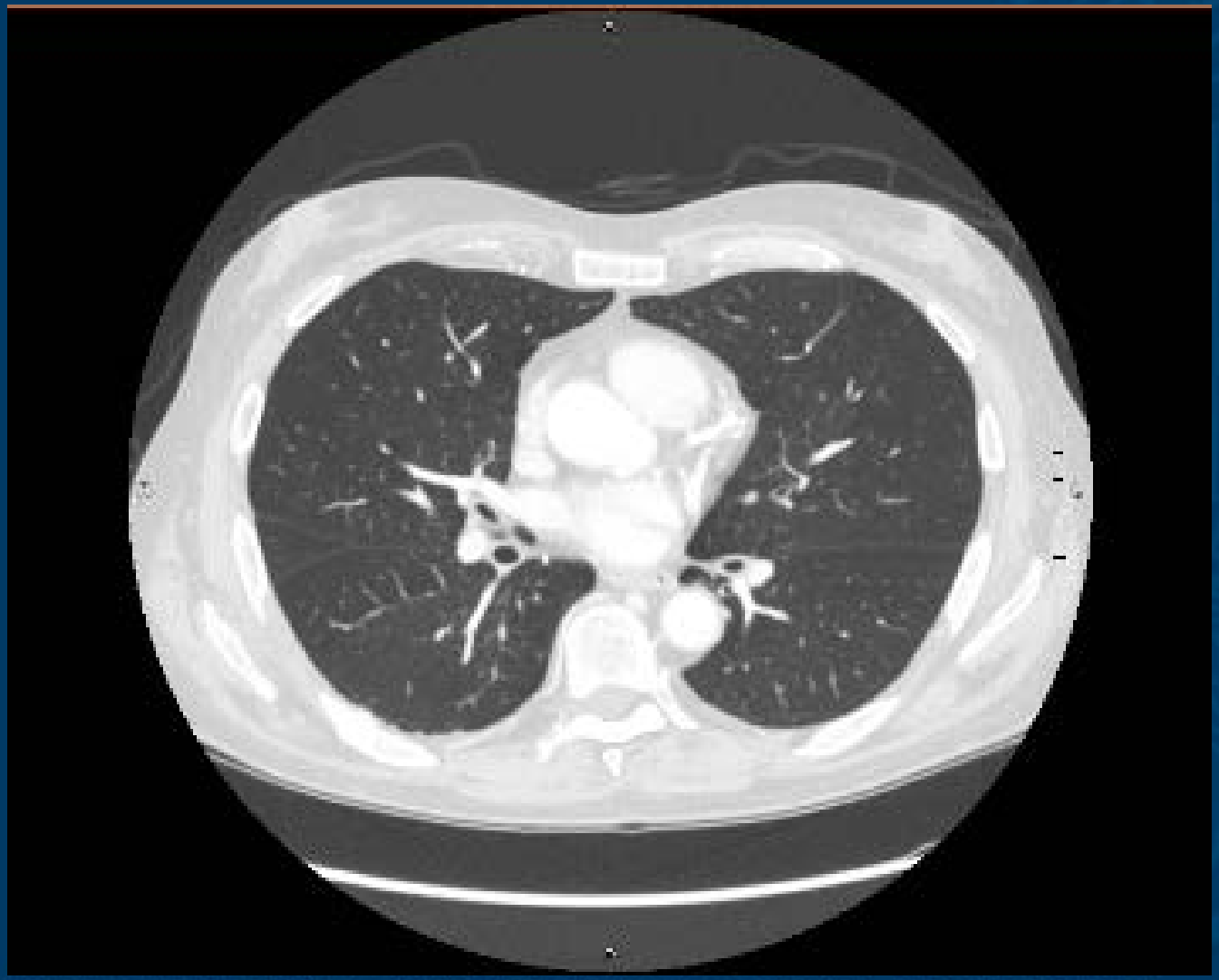
Case 2 Baseline in 3/2017



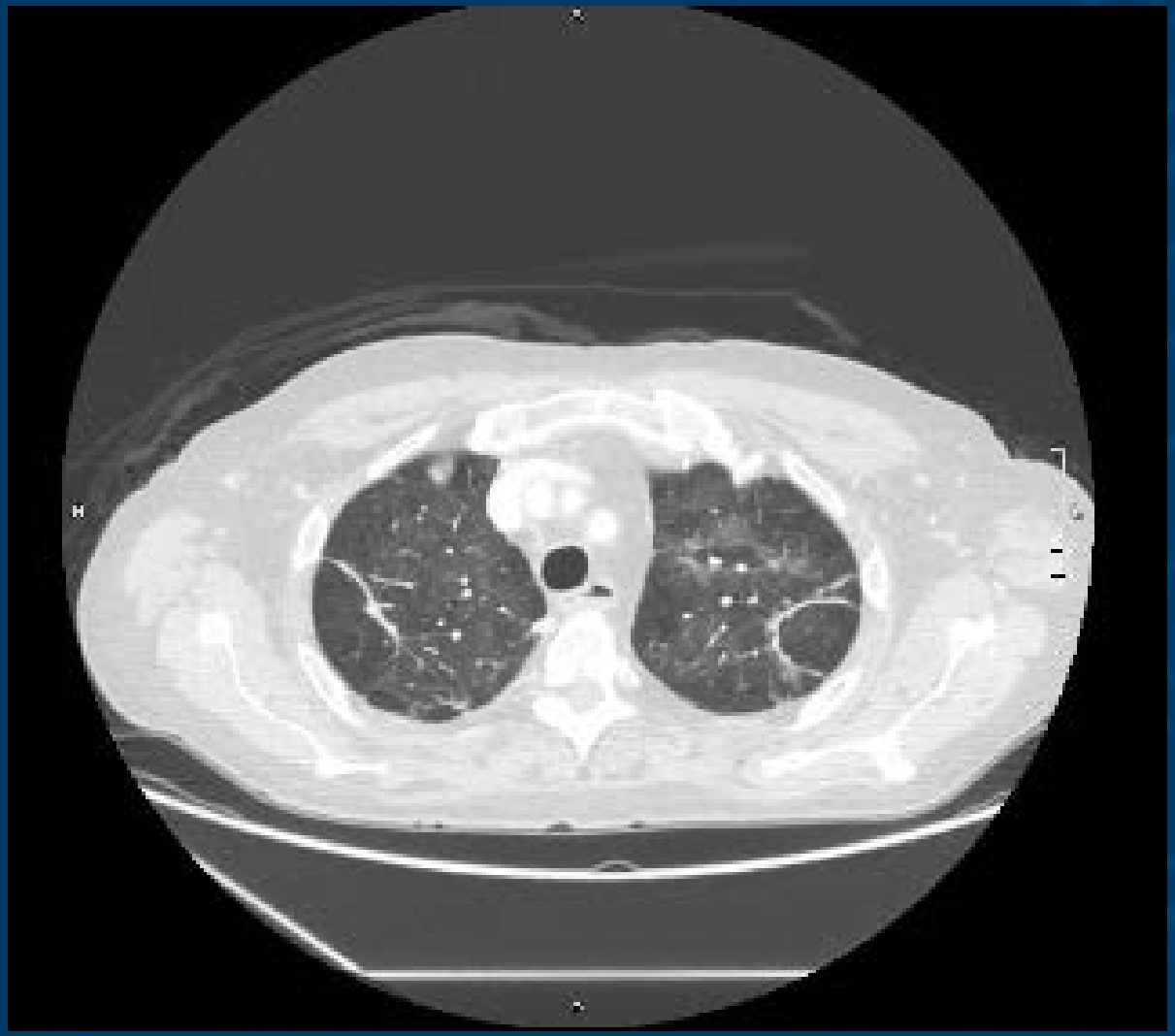
Case 2 Baseline in 3/2017



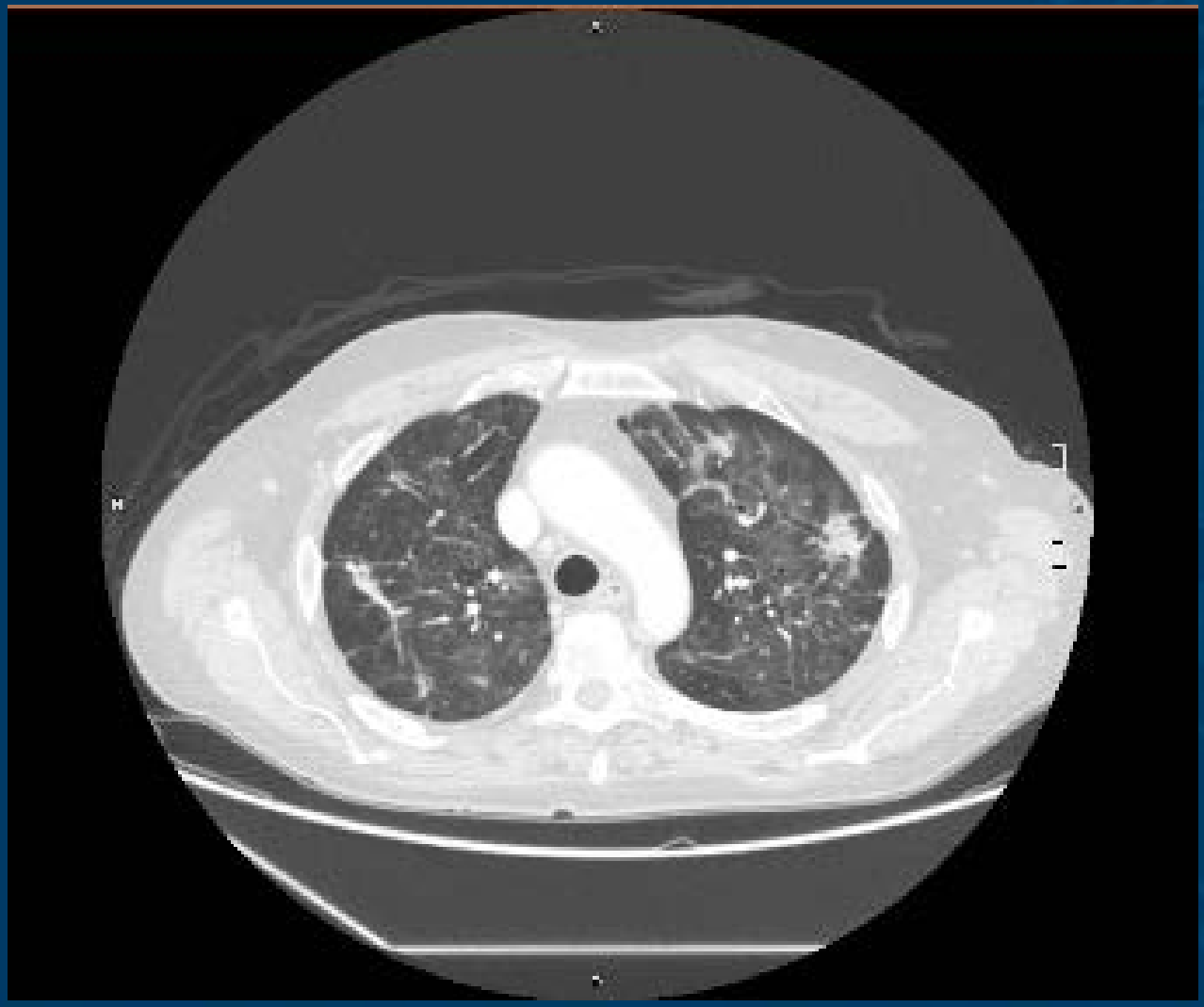
Case 2 Baseline in 3/2017



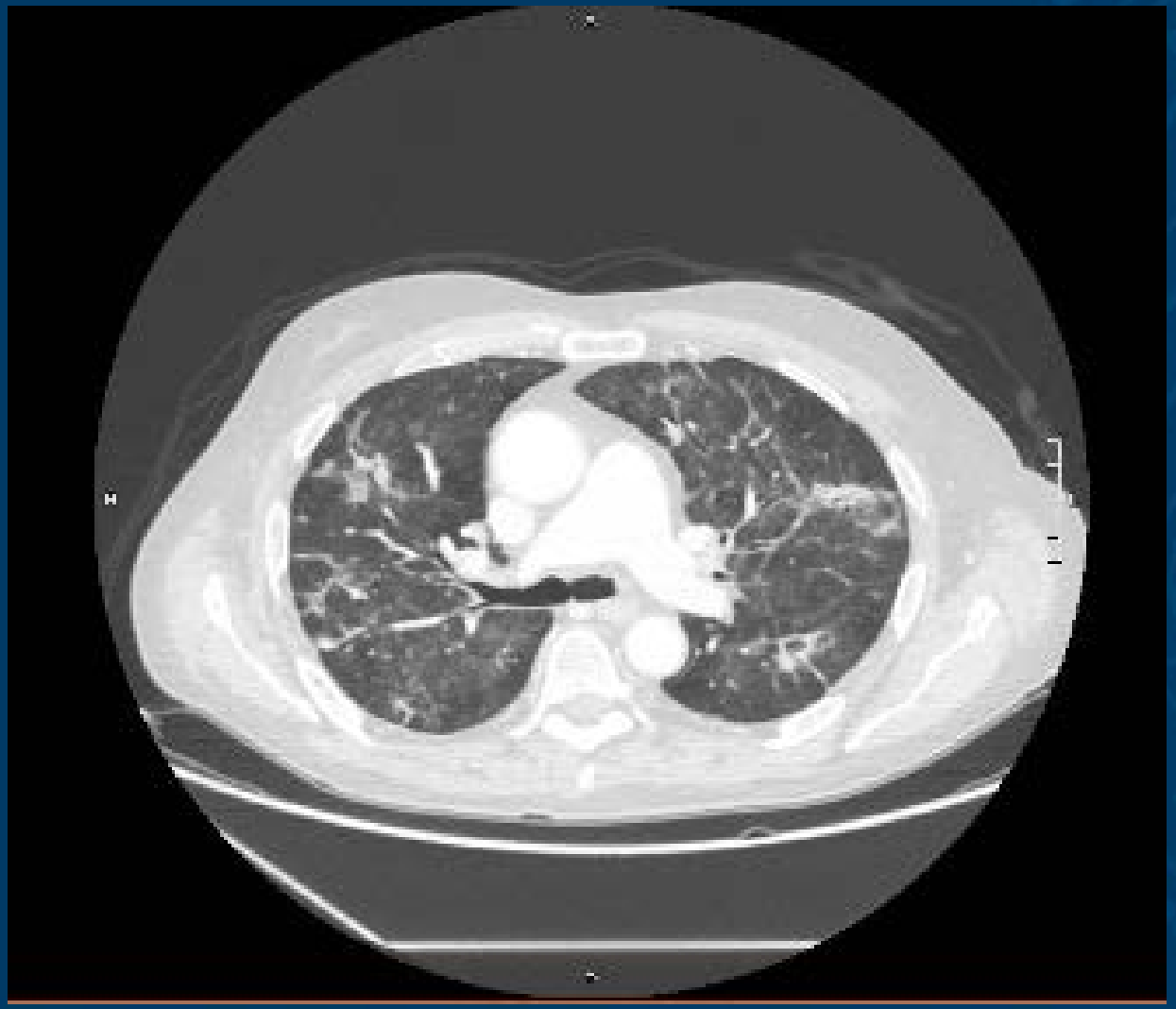
Case 2 in 9/2017



Case 2 in 9/2017



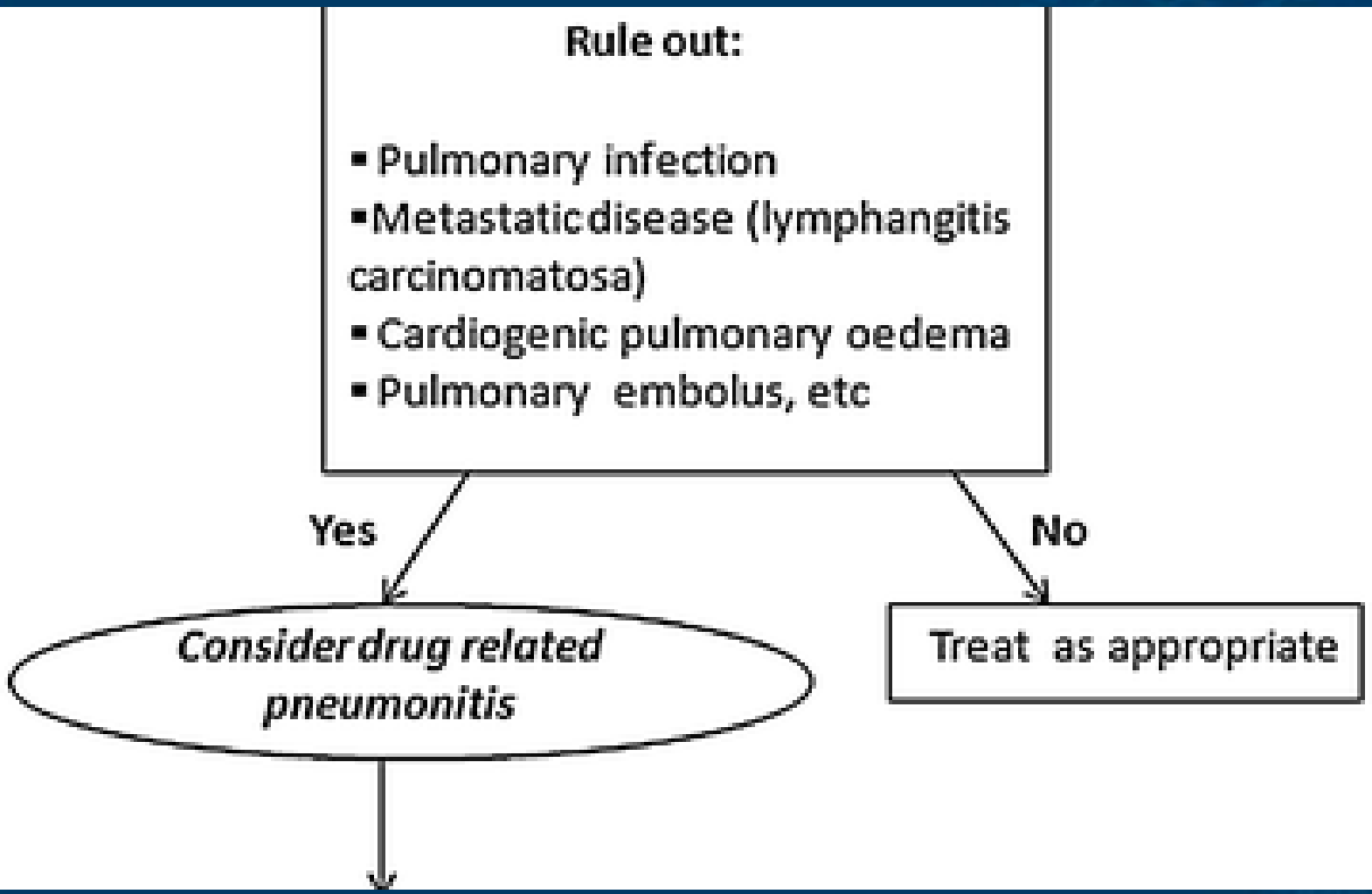
Case 2 in 9/2017



Case 2

- Treated with XRT and adjuvant **docetaxel** (completed 12/2007)
- 2 years on **Goserelin** (LHRH analogues) and **Bicalutamide** (antiandrogens) until 2009
- Multifocal symptomatic brain mets s/p CK
- **Carboplatin / taxotere** → 11/2016 – 1/2017
- New brain mets s/p CK
- Started on **pembrolizumab** in 3/2017

Diagnostic algorithm of pneumonitis



So lets consider these newer targeted agents?

1. **TKIs: EGFR**
2. **mTOR inhibitors**
3. **PD-1 and PD-L1 inhibitors**

TKIs and ILD

- 1st case reported in 2003 in Lancet – Gefitinib
- Multiple reports since then

	DAD	BO	COP	HP	IP
Gefitinib	+ +			+	+
Erlotinib		+	+	+	
Sorofenib		+	+		+

Min, J.H., Lee, H.Y., Lim, H. et al. Cancer Chemother Pharmacol (2011) 68: 1099.

mTOR inhibitors

- Sirolimus
- Everolimus
- Temsirolimus

PD-1

Anti-PD-1 monoclonal antibodies

- Nivolumab
- Pembrolizumab (previously lambrolizumab)
- Pidilizumab

Anti-PD-L1 mAbs

- Durvalumab
- Atezolizumab

PD-1 and PD-L1 mAbs

Toxicities with anti-PD-1/PD-L1 mAbs appear to be less common and less severe

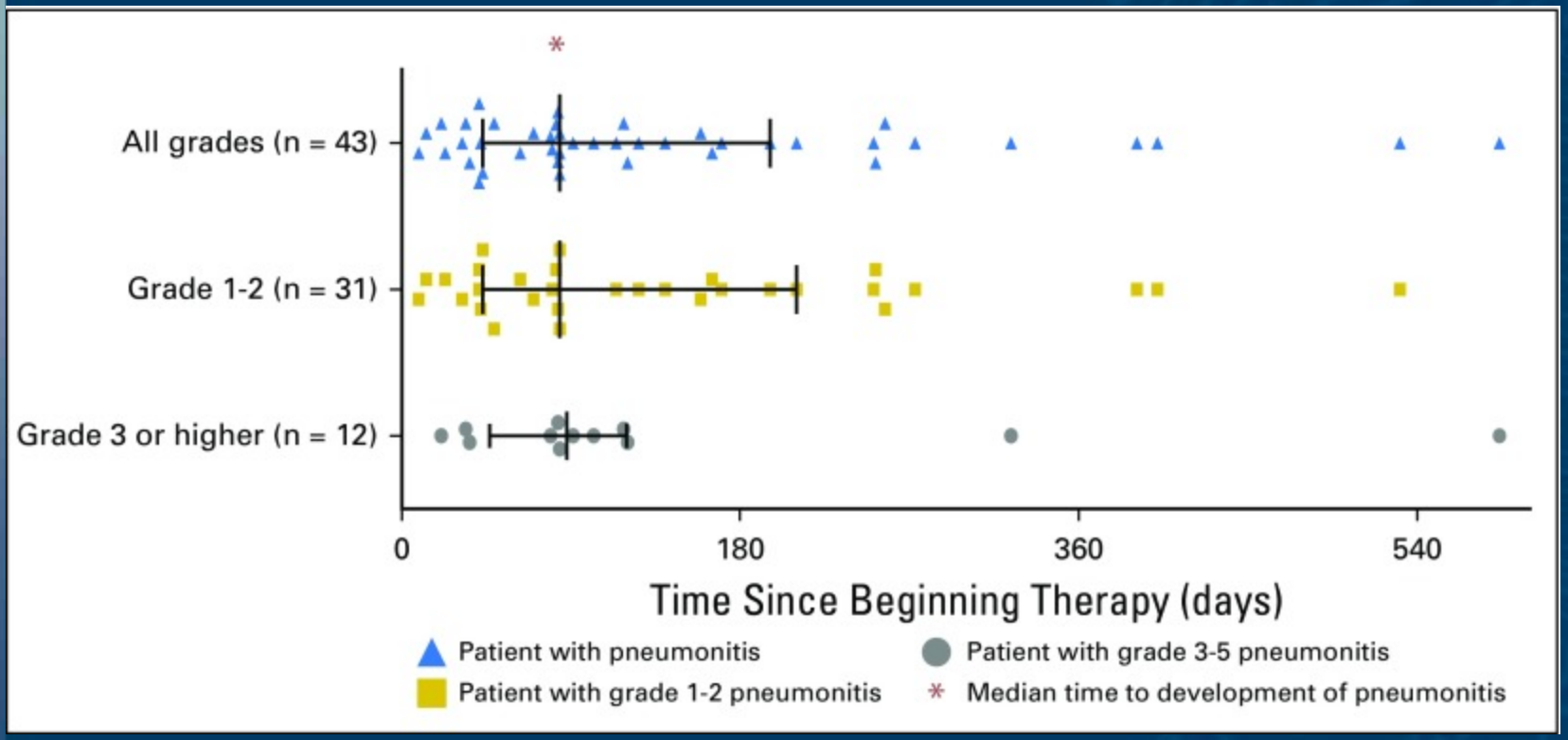
- 7% to 12% in patients receiving single-agent anti-PD-1/PD-L1 mAbs

PD-1 and PD-L1 mAbs

Adverse events of anti-PD-1/PD-L1 therapy

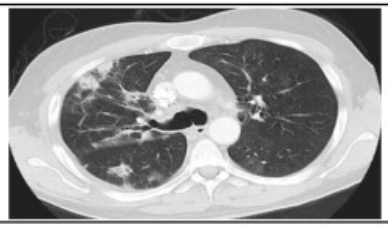
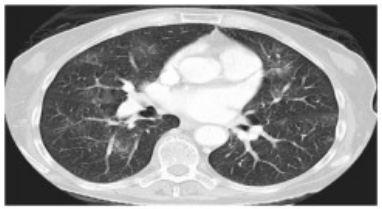
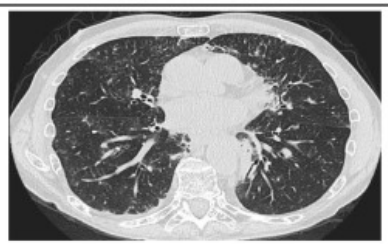
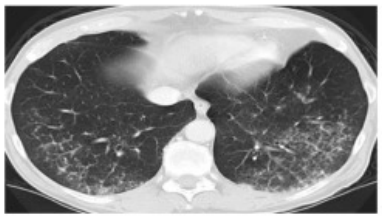
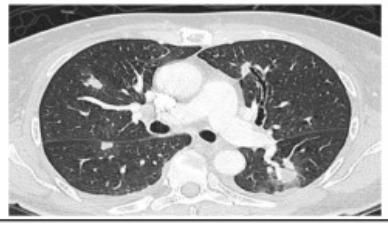
- **Fatigue**
- **Pyrexia, chills, infusion reactions**
- Skin rash (maculopapular, papulopustular, Sweet's syndrome, follicular, or urticarial dermatitis)
- **Diarrhea/colitis**
- **Endocrine toxicities (**hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, and adrenal insufficiency)
- **Hepatic toxicities (**elevations in AST and ALT levels)
- **Pneumonitis**

Time to development of pneumonitis after starting PD-1 or PD-L1 inhibitor



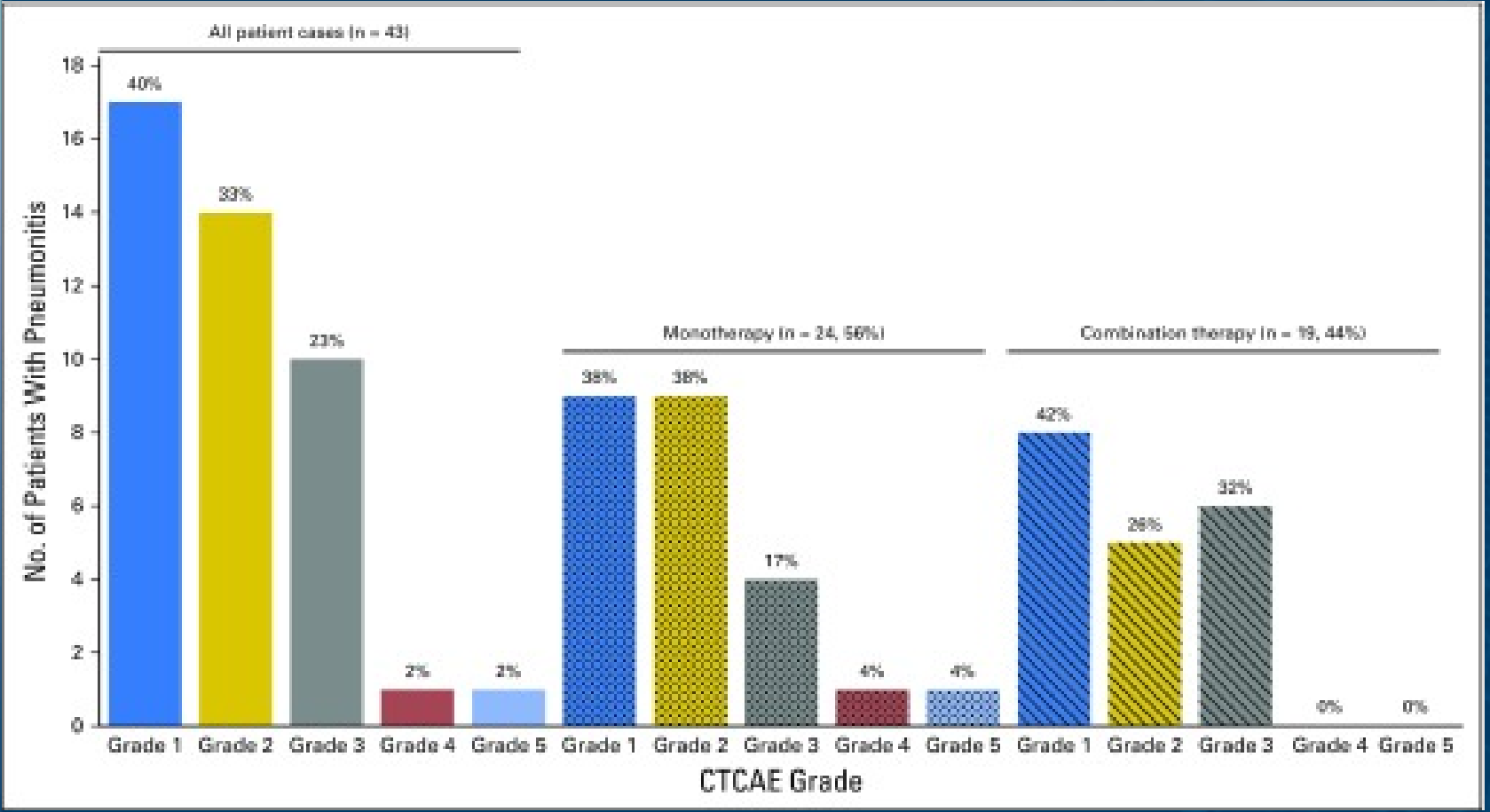
J Clin Oncol. 2017 Mar 1; 35(7): 709–717.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5559901/

Radiographic pattern of pneumonitis on PD-1 or PD-L1

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

J Clin Oncol. 2017 Mar 1; 35(7): 709–717.

Grade of pneumonitis on PD-1 or PD-L1 inhibitor



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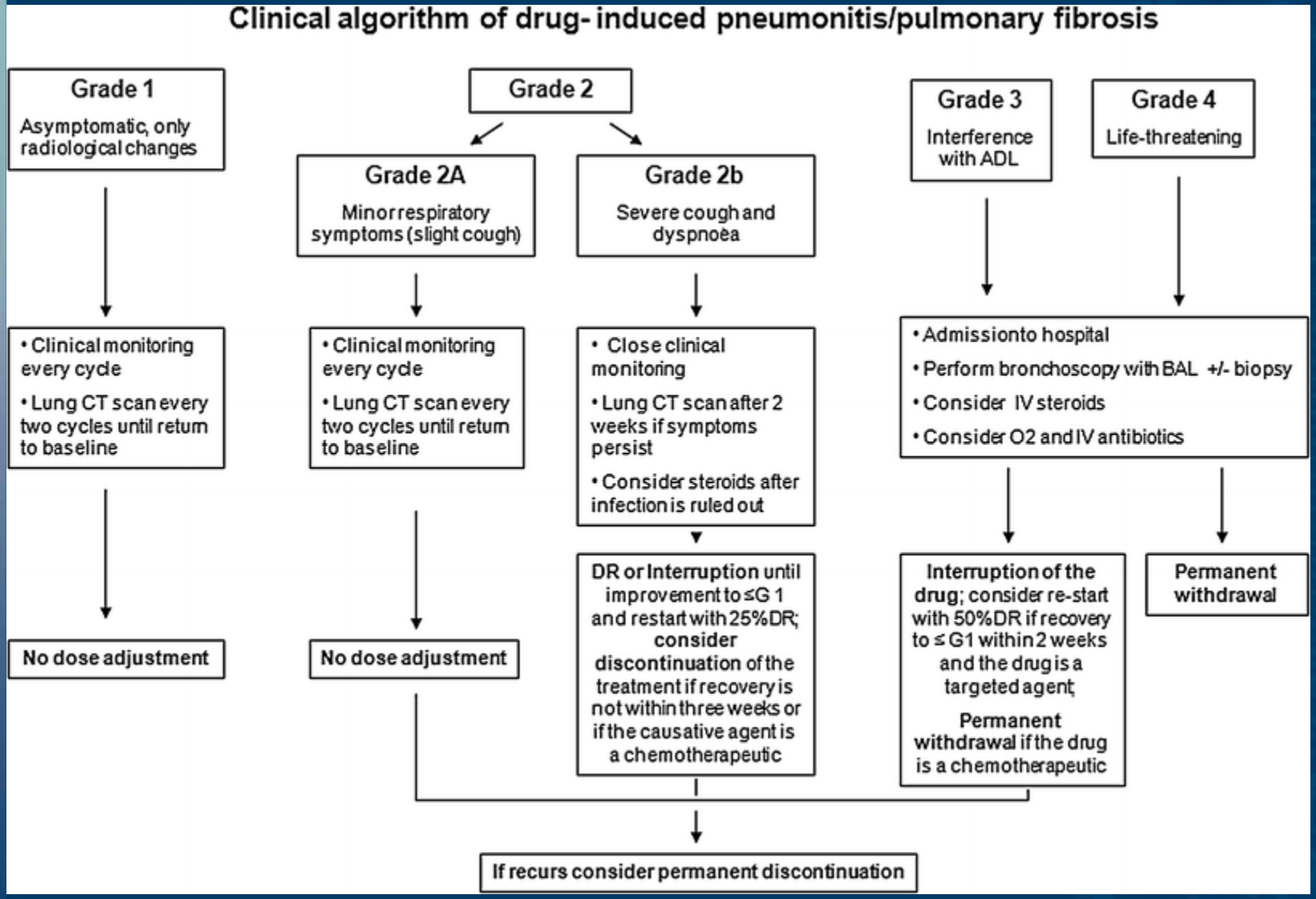
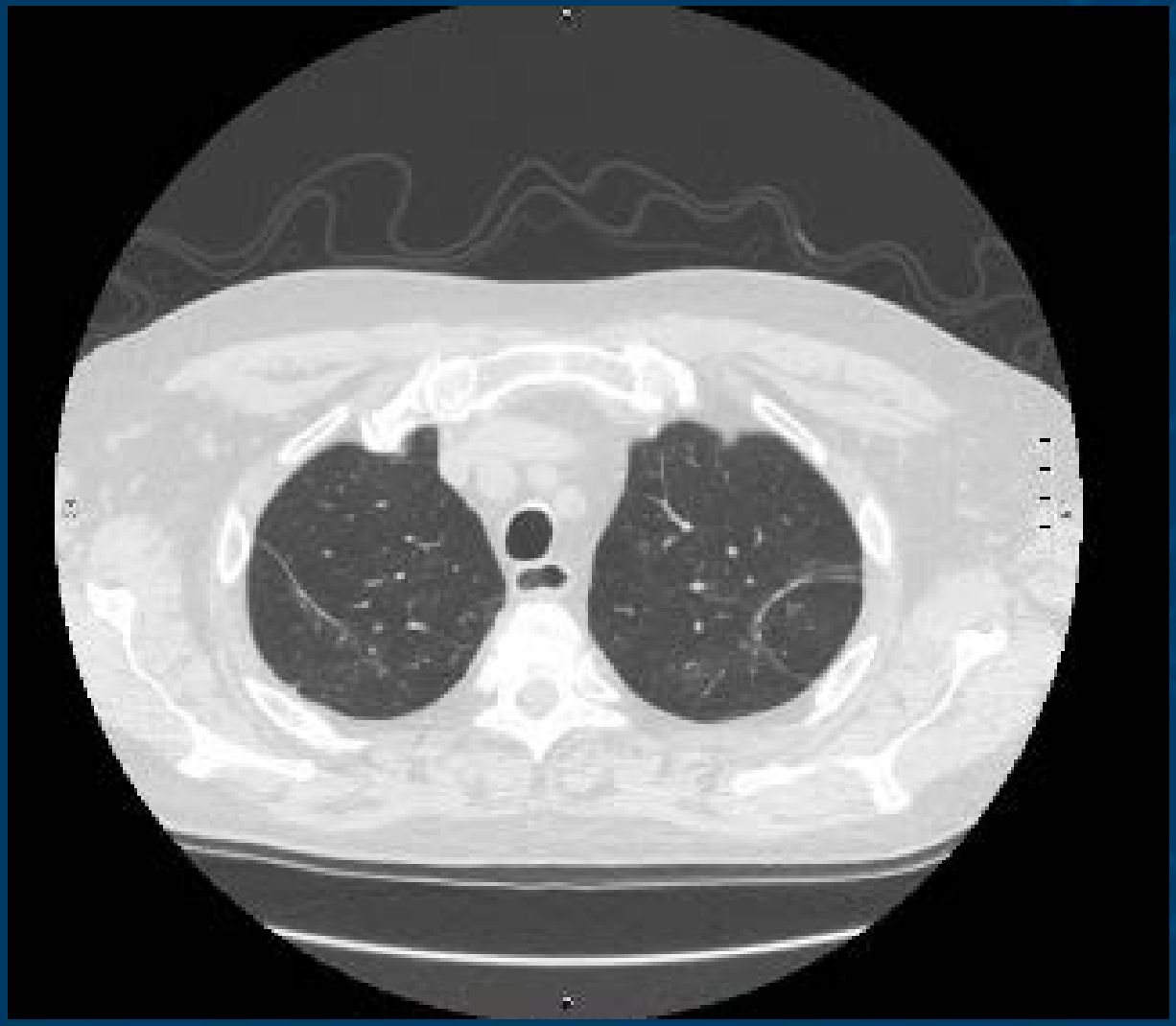


Omarini, C., Thanopoulou, E. & Johnston, S.R.D. Breast Cancer Res Treat (2014) 146: 245. https://doi.org/10.1007/s10549-014-3016-5

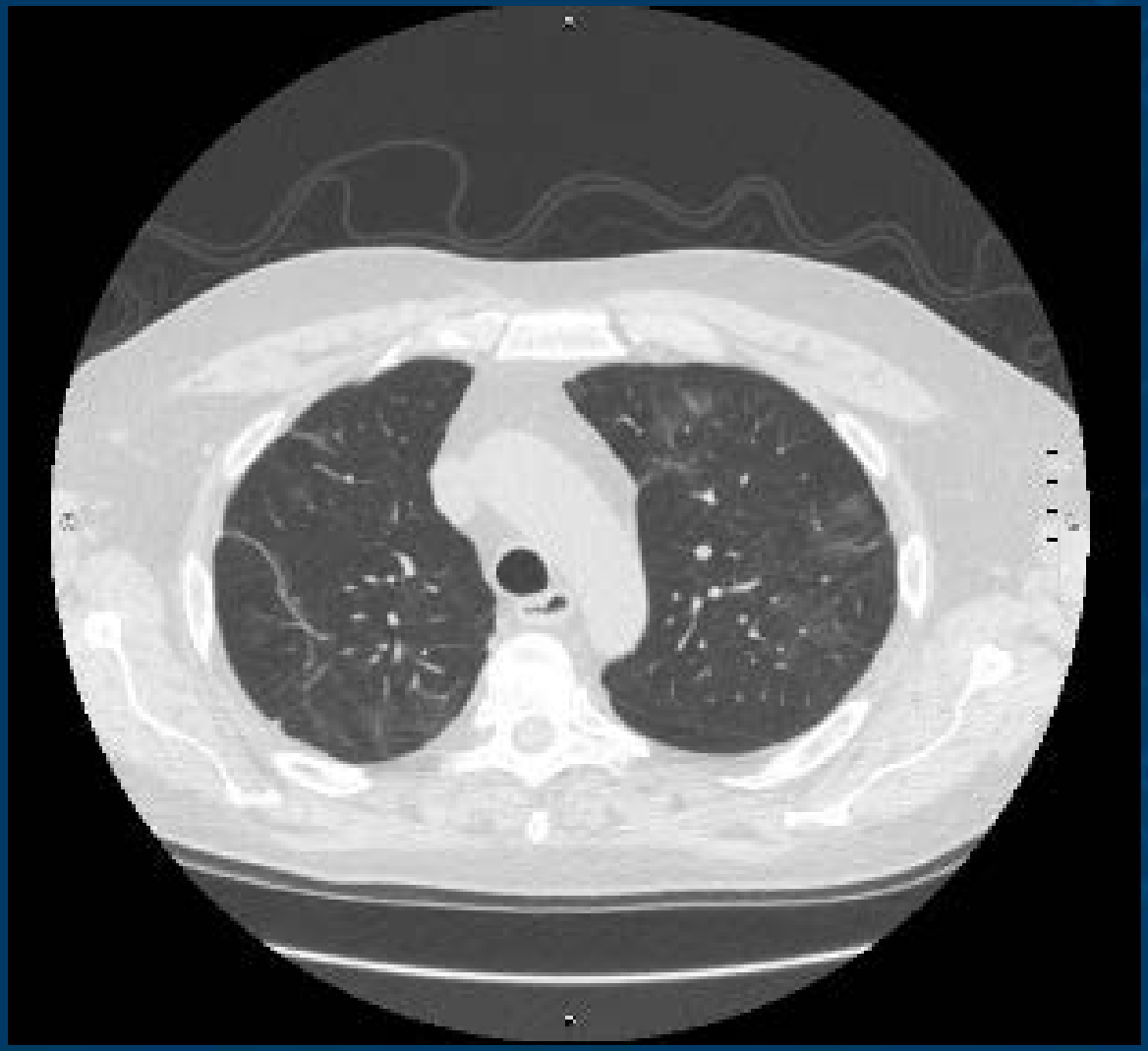
Case 2 – Follow up

- Treated with **Prednisone** – initially 70 mg (1 mg / kg) daily and slowly tapered over 4 months
- 1/2018 **pembrolizumab** restarted

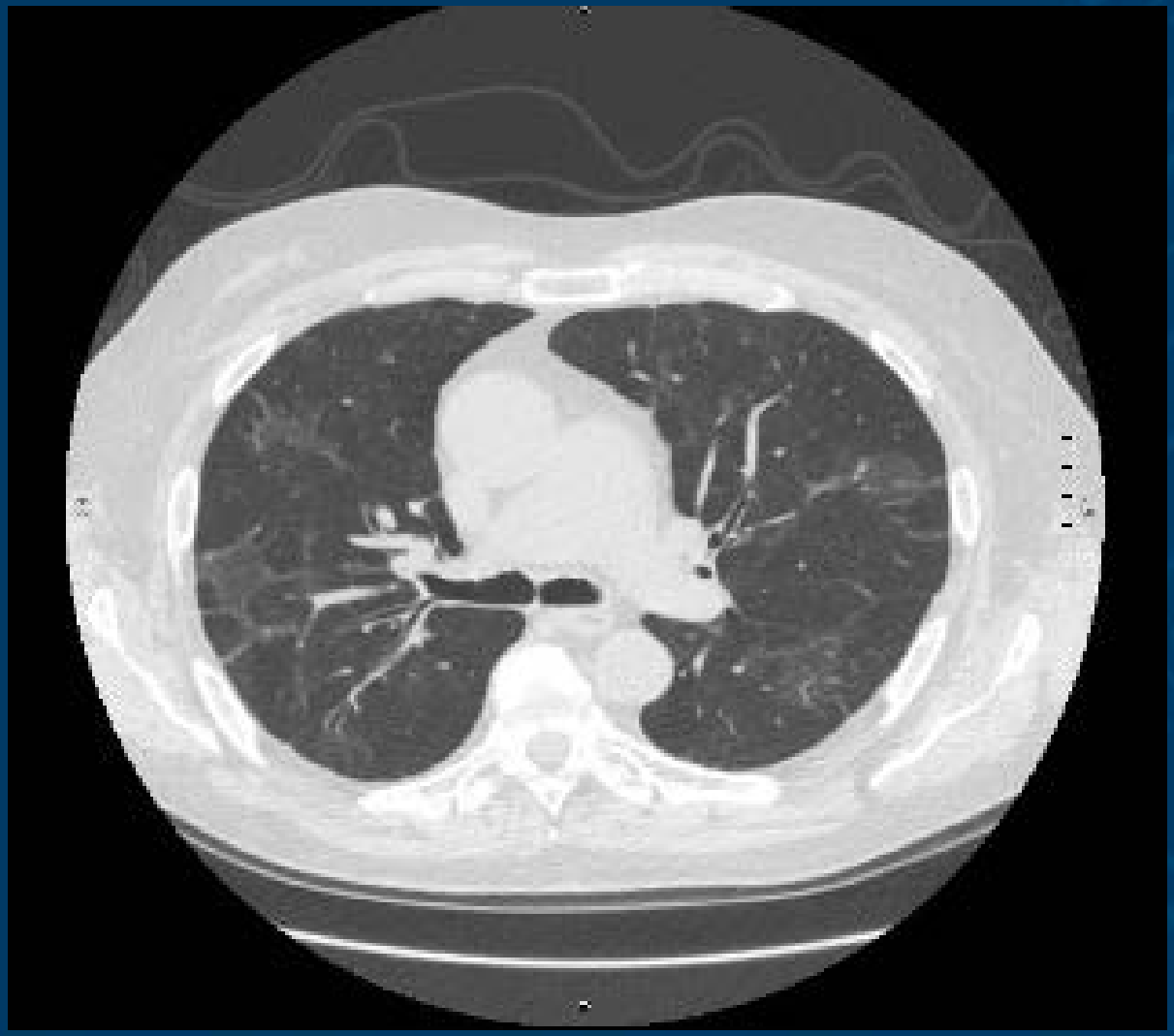
Case 2 – October 2017



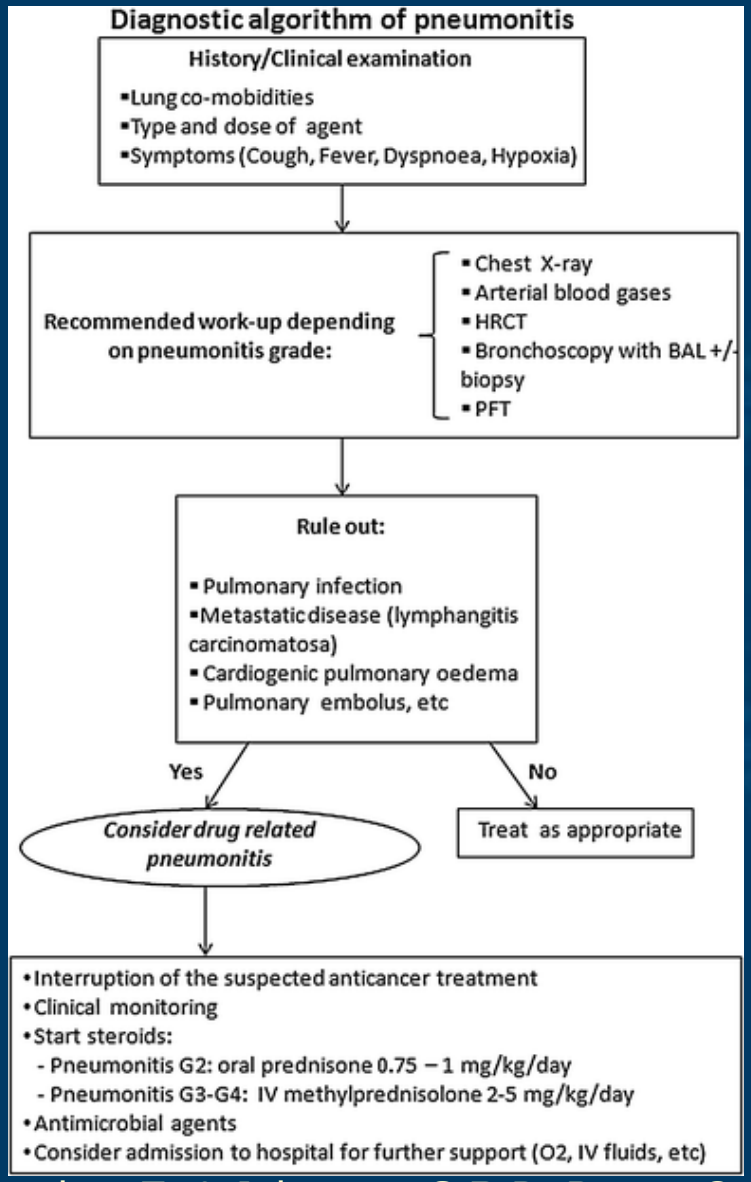
Case 2 – October 2017



Case 2 – October 2017



Take Home Points from Diagnosis / Management of Drug Induced Pneumonitis



Omarini, C., Thanopoulou, E. & Johnston, S.R.D. Breast Cancer Res Treat (2014) 146: 245. https://doi.org/10.1007/s10549-014-3016-5

A question for you…

54 year old woman who has been responding to treatment with pembrolizumab for lung cancer now develops Grade 1 drug induced pneumonitis. *Which of the following is the most appropriate recommendation?*

A. Stop pembrolizumab permanently

B. Hold pembrolizumab. If symptoms imaging improves within 1 week, resume therapy.

C. Continue pembrolizumab with 50% dose reduction.

D. No dose adjustment if needed. Continue to monitor clinically and with repeat chest CT scans.

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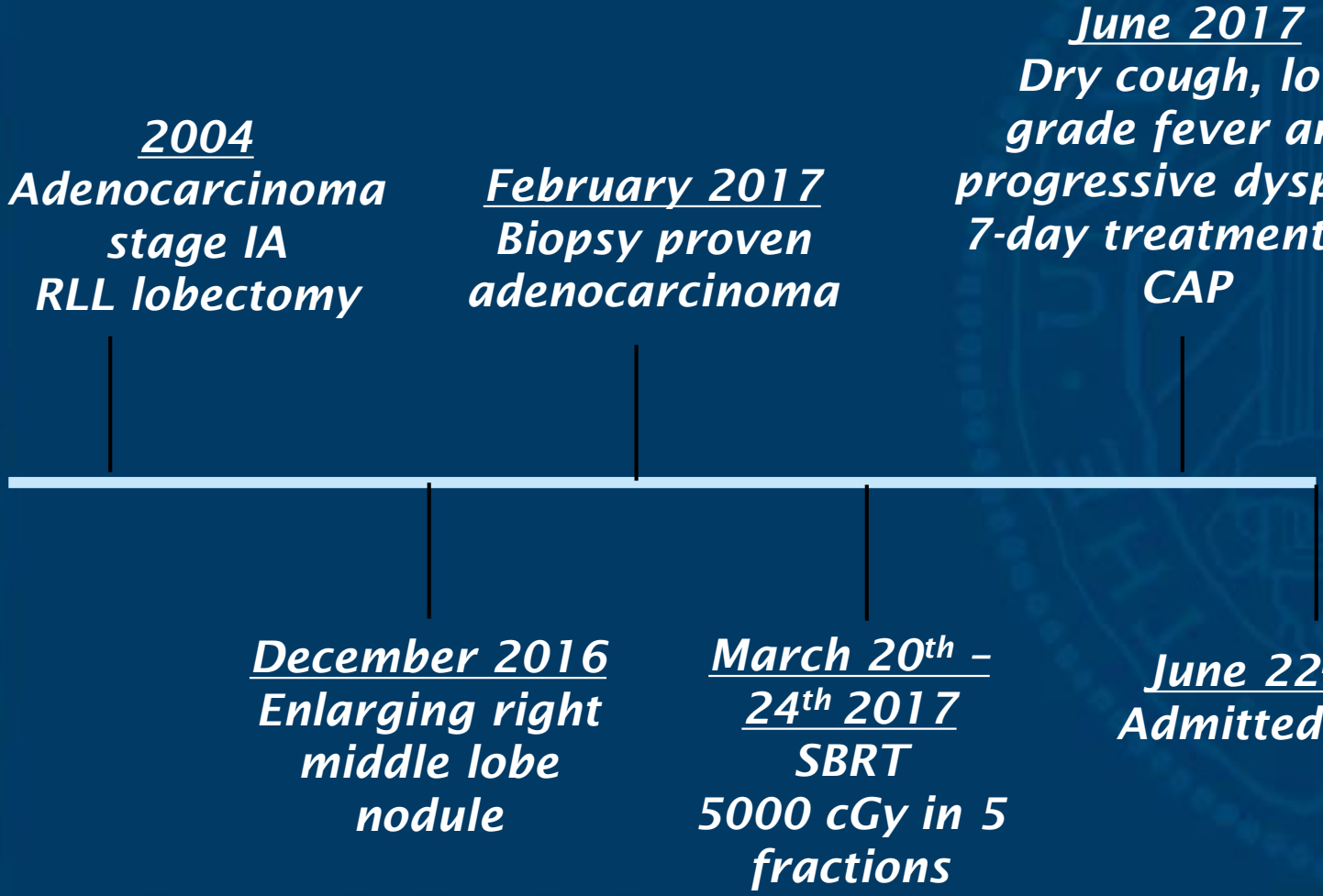
Grade	Presentation	Diagnostic Testing	Management	Follow up
1	Asymptomatic with Radiographic changes only	Chest CT scanning Consider Bronch +/- other microbial assessment	Continue therapy Monitor sx q3 days	Repeat Chest CT after every cycle or if develops sx.
2	Mild / Moderate new symptoms		HOLD therapy Monitor sx daily Oral prednisone (1mg/kg/d)	If improves to ≤ Grade 1 w/in 3 days, resume therapy. If persists, stop therapy. Taper steroids over 1+ mo.
3-4	Severe or life threatening Worsening hypoxia		STOP therapy Hospitalize IV methylpred 2-4 mg/kg/d	After sx improve to ≤ Grade 1, taper steroids over 6+ wks If worsens, consider additional immuno-suppression

Case 3:

Special Thanks to UCSF Clinical Fellow
Shoshana Zha

Case 3:
78 year-old man presenting with worsening dyspnea



Special thanks to Shoshana Zha, MD for case / slides

Case 3: Additional History

PMH

- Type-II DM
- CAD s/p CABG 6/2016, persistent L pleural effusion
- CHF (EF 50-55%)
- A-fib & sick sinus with pacemaker
- HTN
- CKD stage IV
- COPD: FEV1 1.4 (67%)

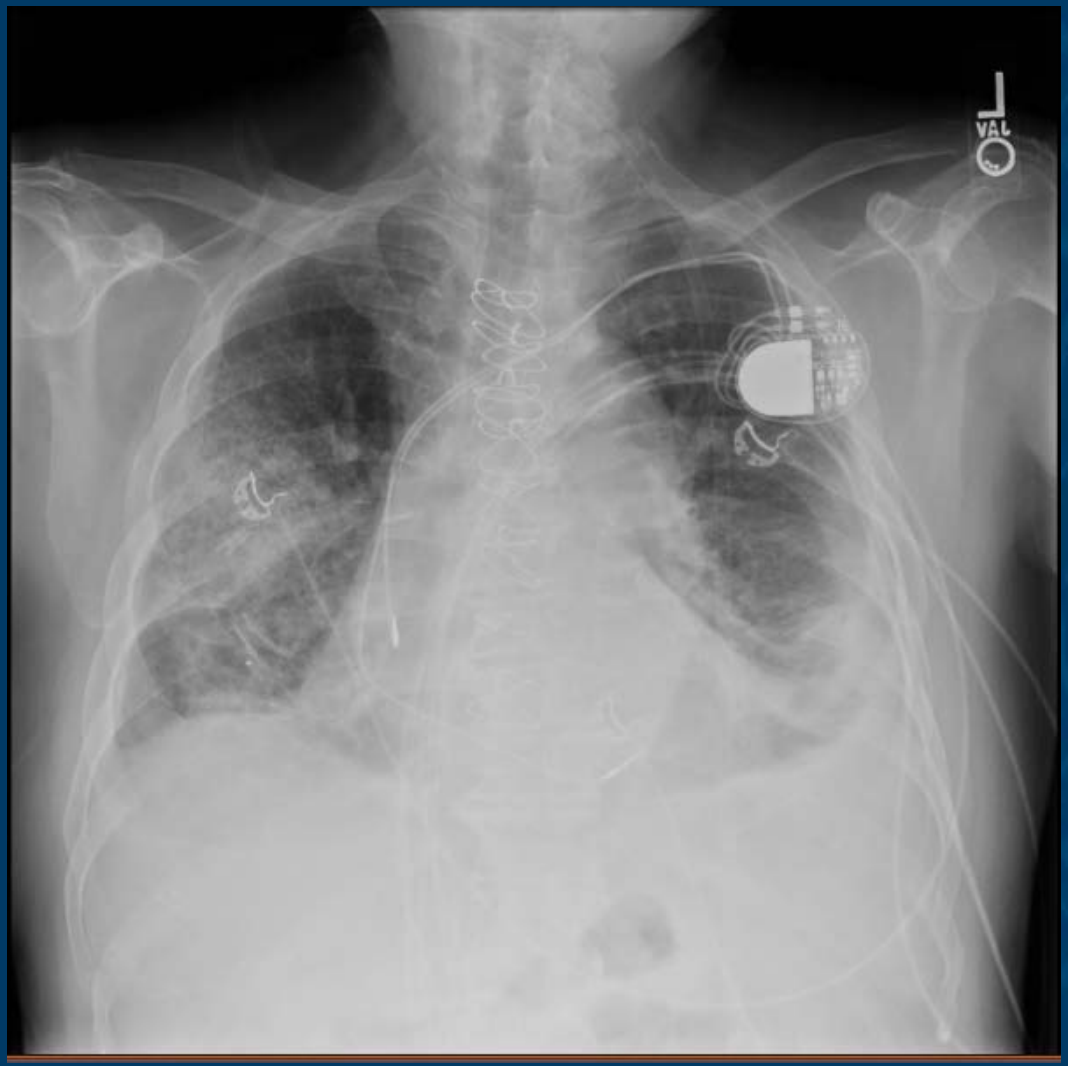
MEDICATIONS

- ASA
- Atorvastatin
- Metoprolol XL
- Bumex 2mg BID
- Coumadin
- Glargine
- Pioglitazone
- Repaglinide
- Spiriva daily,
- Albuterol PRN

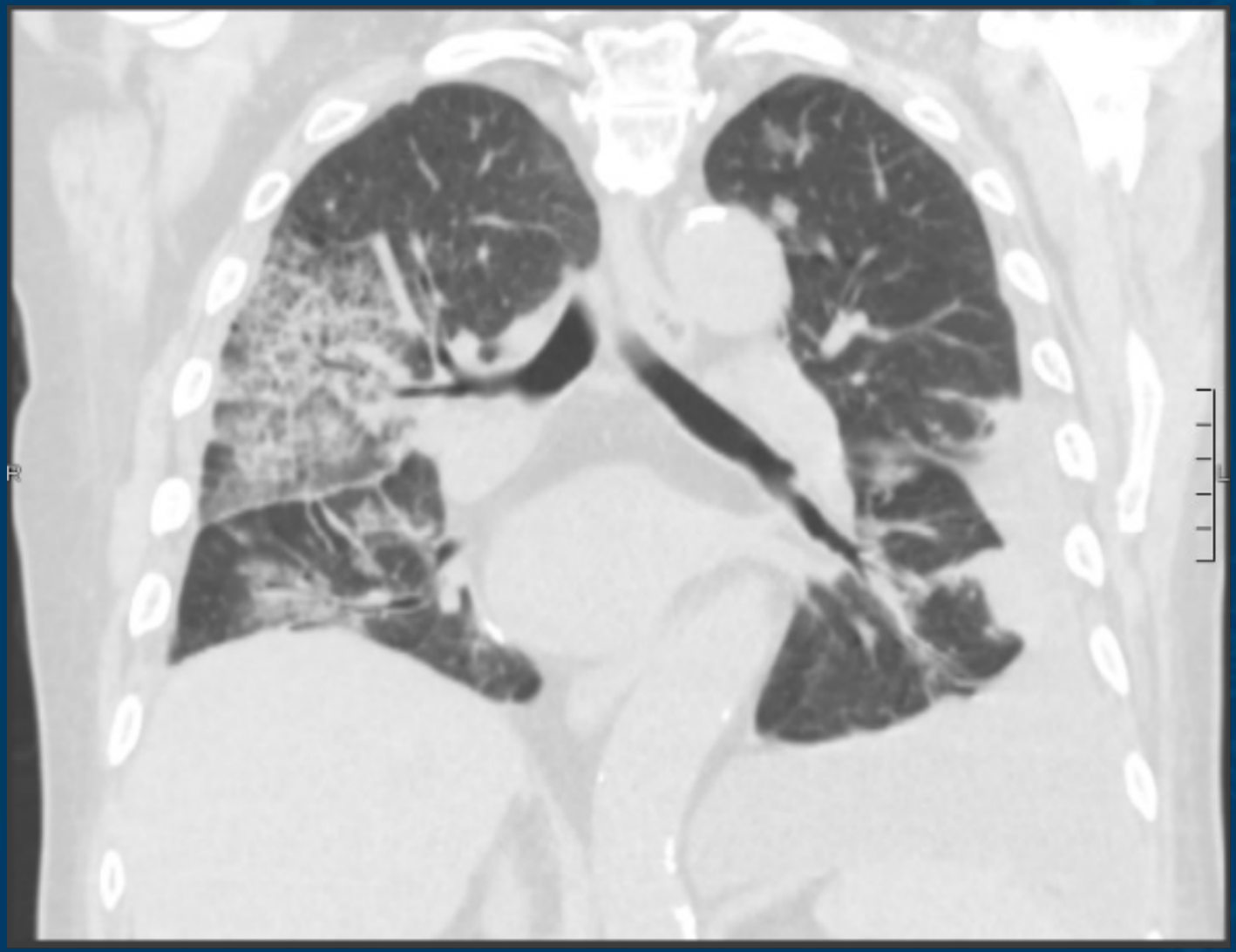
SH:

- Smoked 50-60 pack years, quit ~2003
- Occasional alcohol
- No illicit drug use

Special thanks to Shoshana Zha, MD for case / slides



Special thanks to Shoshana Zha, MD for case / slides



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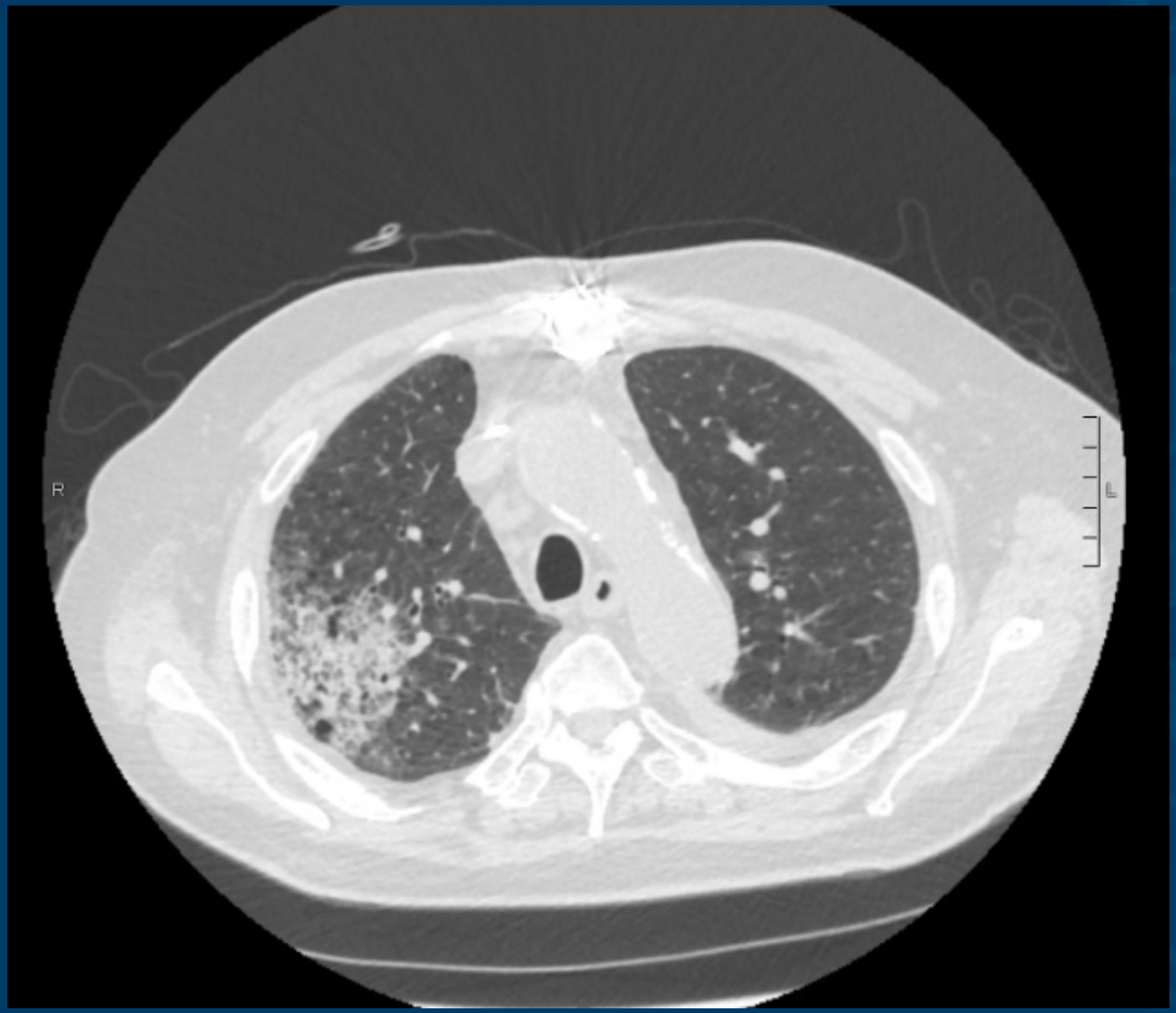

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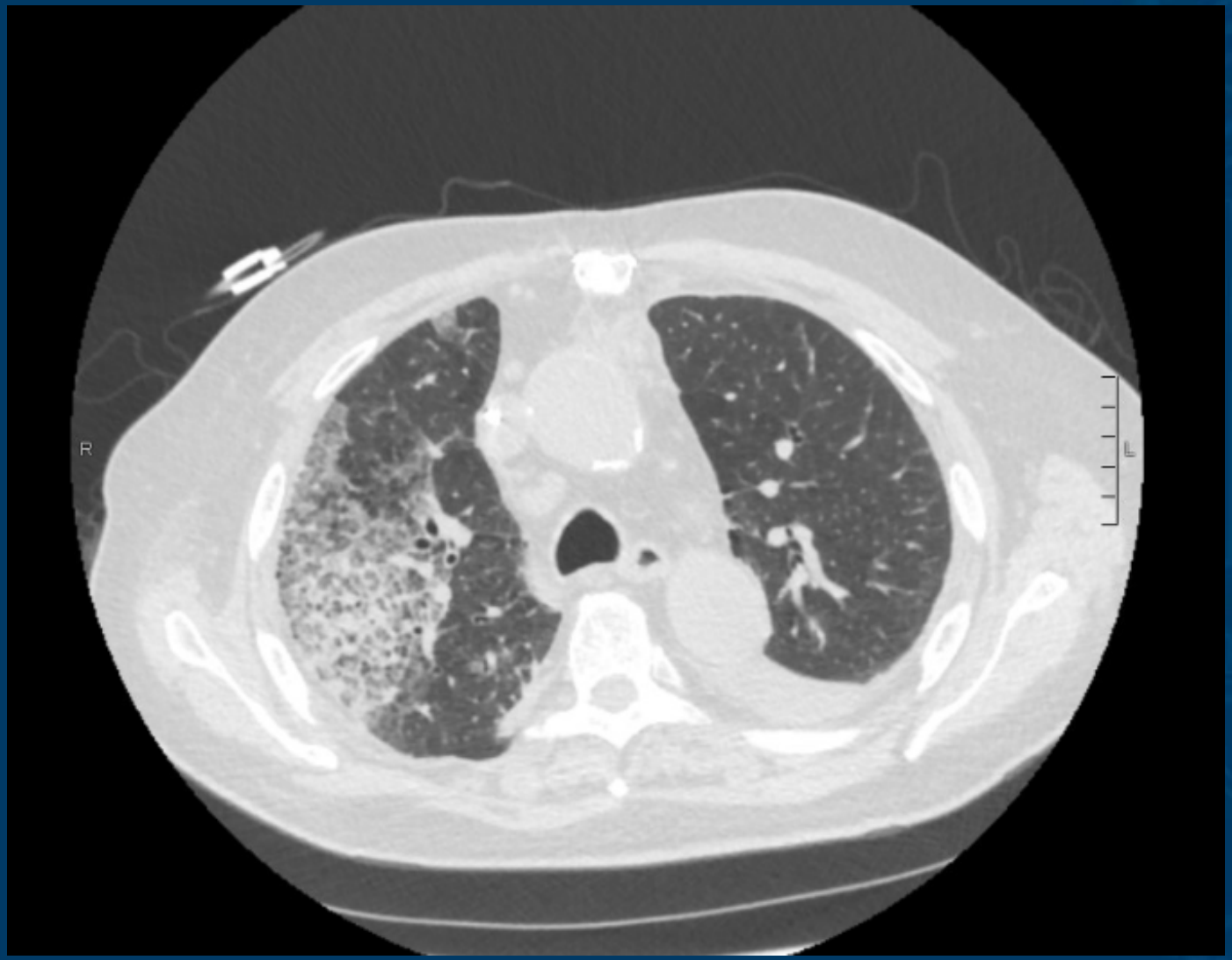

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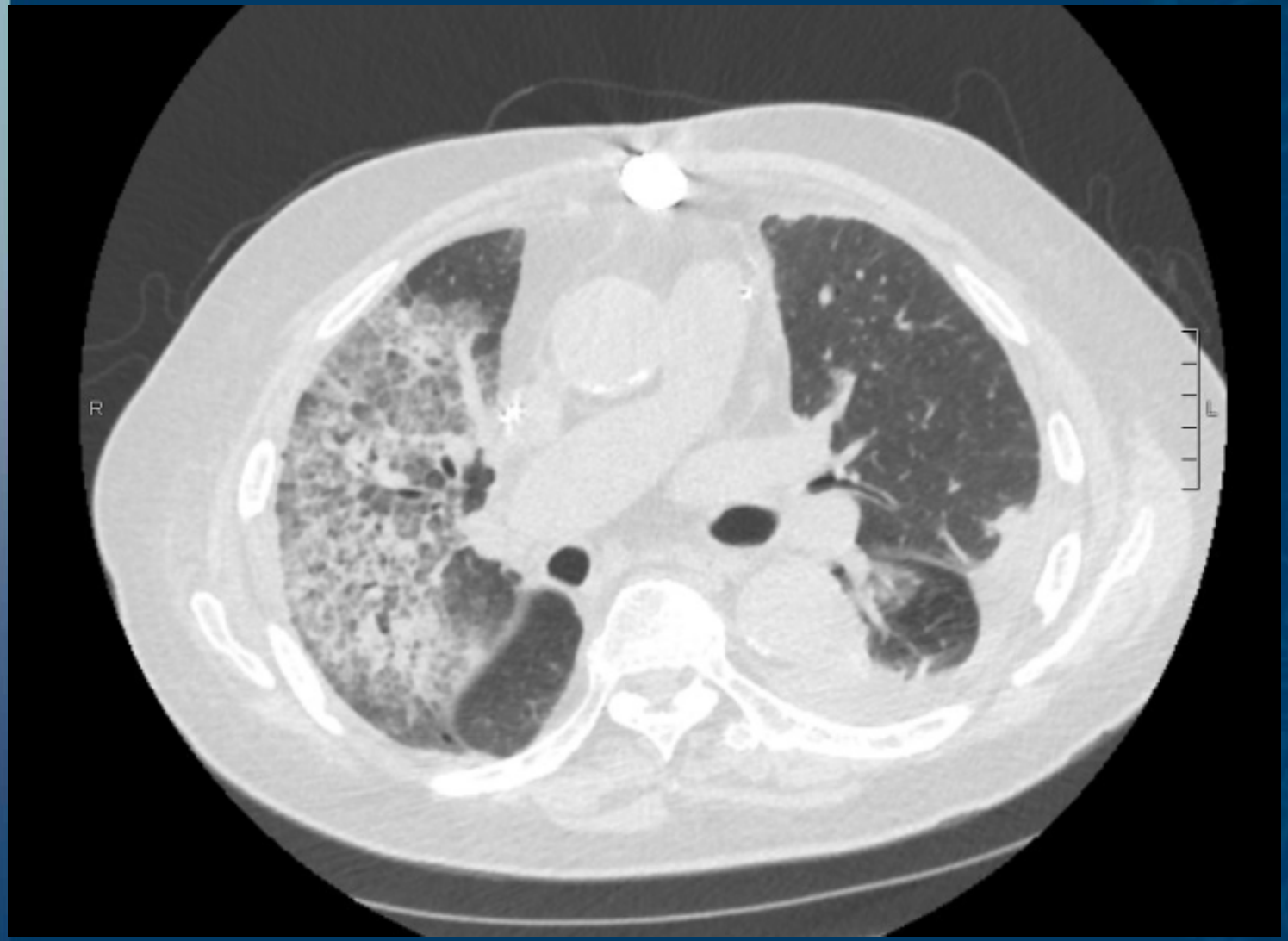


Special thanks to Shoshana Zha, MD for case / slides

Case 3: Differential diagnosis

- Infection
- Radiation pneumonitis
- Organizing pneumonia
- Diffuse alveolar hemorrhage
- Hypervolemia
- Malignancy

Special thanks to Shoshana Zha, MD for case / slides

Case 3: Workup/management

- Started steroids 60mg/day and levofloxacin
- Bronchoscopy without sign of infection or DAH
- Began to improve
- Steroids tapered: 60mg x 6days → 40mg x 3 days → 20mg daily in setting of rapid improvement + difficult glycemic control
- Discharged on 20mg/day to be taken until follow-up

Special thanks to Shoshana Zha, MD for case / slides

Case 3: To ED 34 days later

- 2-weeks of worsening dyspnea on exertion
- Low-grade fever
- Non-productive cough
- Chest pressure
- In ED, hypoxic to 82% on room air

Special thanks to Shoshana Zha, MD for case / slides

Case 3: Physical exam

- Vitals: BP 104/53, HR 84, RR 20, O2 Sat 96% on 10LPM supplemental oxygen
- CV: Irregularly irregular. PMI displaced laterally. No murmurs. JVD 7 cm at 30 degrees. Trace edema BLE.
- Resp: Speaking in 3-4 word sentences. Bibasilar crackles.

Special thanks to Shoshana Zha, MD for case / slides

Case 3: Laboratories/data

VBG (ABG not obtained): 7.46 / PCO2 45/

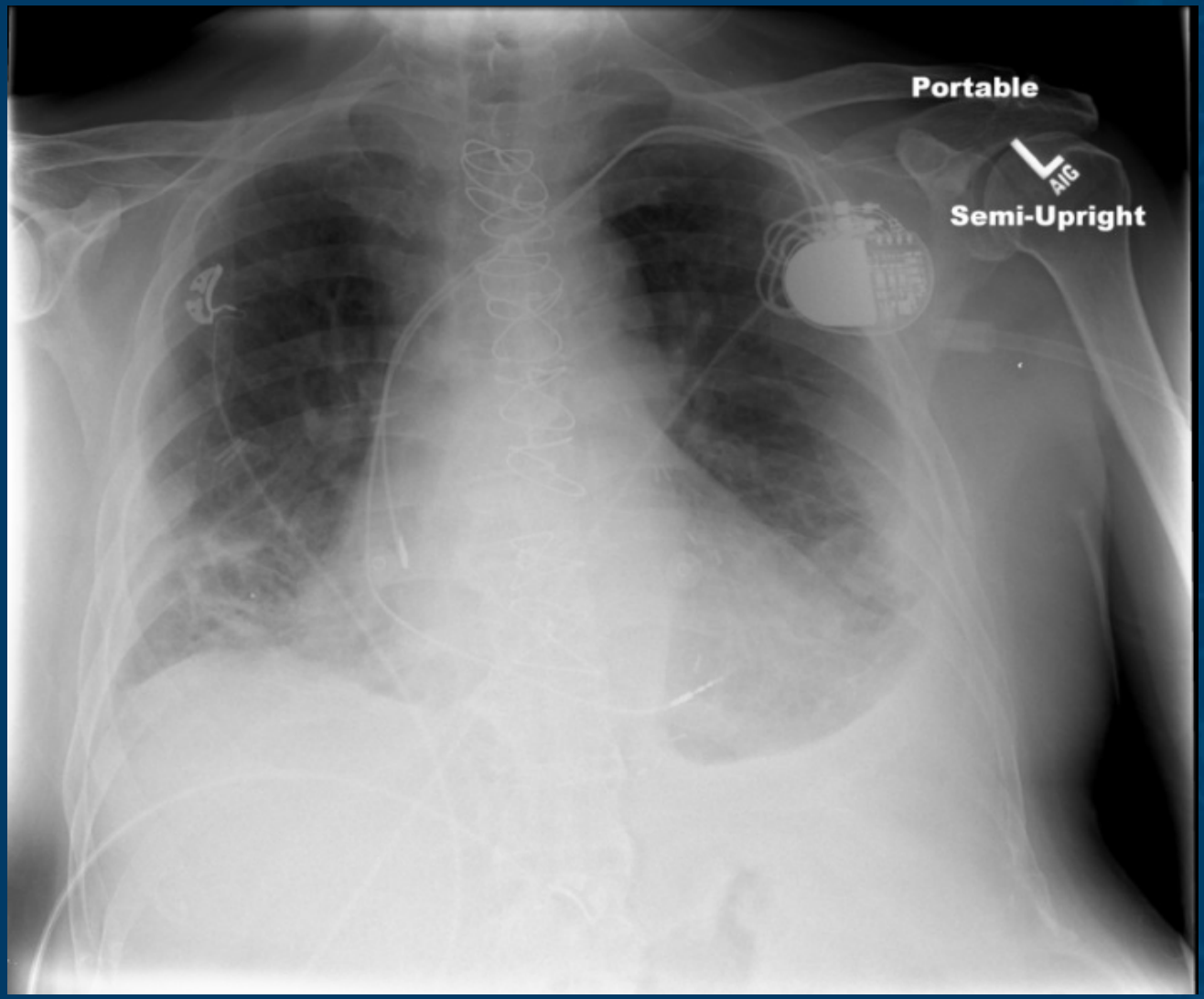
BUN 30, Cr 1.55 (baseline 1.3), Electrolytes WNL

WBC 12.2 with 10.45 N, 0.68 L, 0.84 M, 0.15 E

LFTs WNL

Troponin 0.1, EKG without significant changes

Special thanks to Shoshana Zha, MD for case / slides



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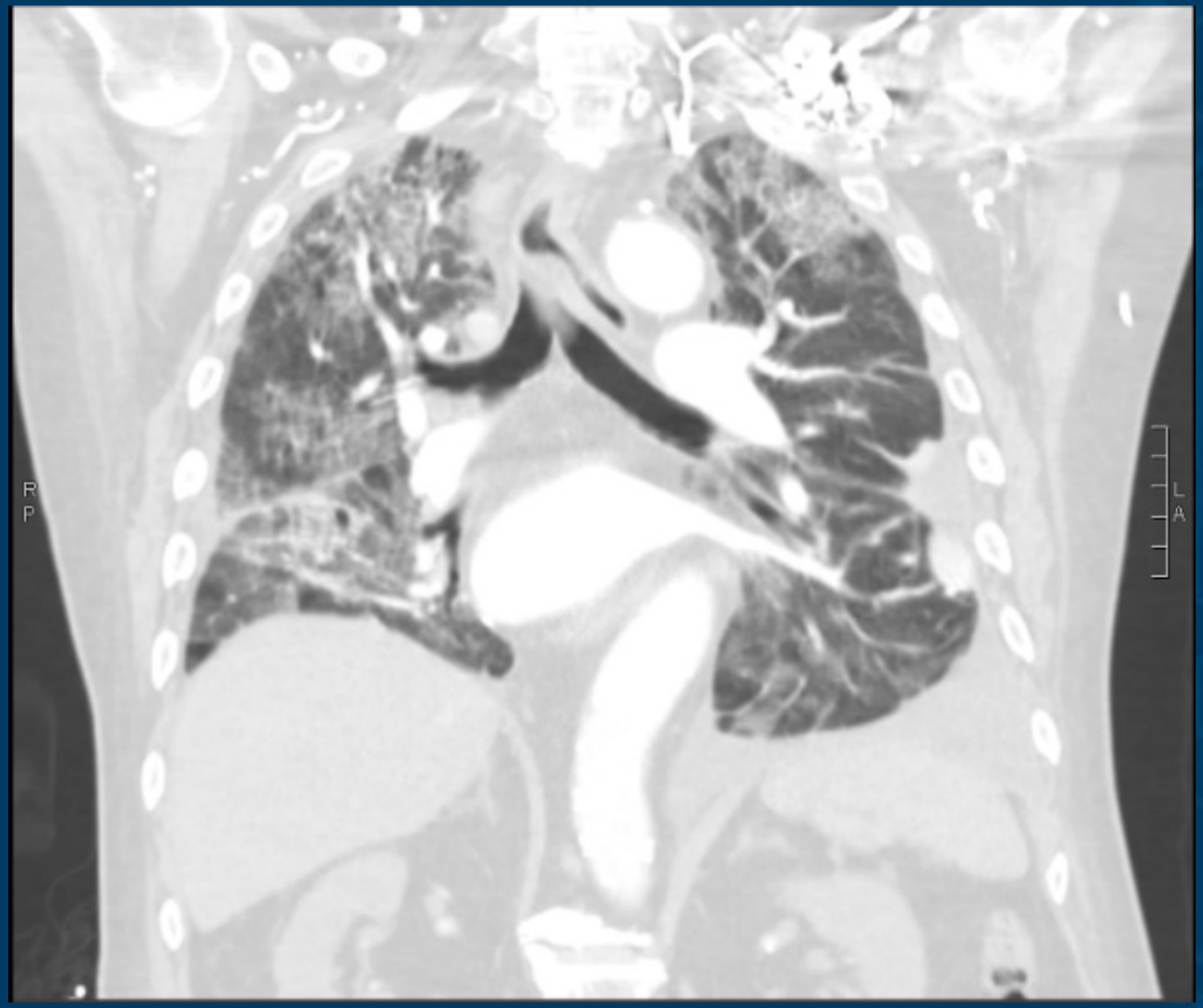

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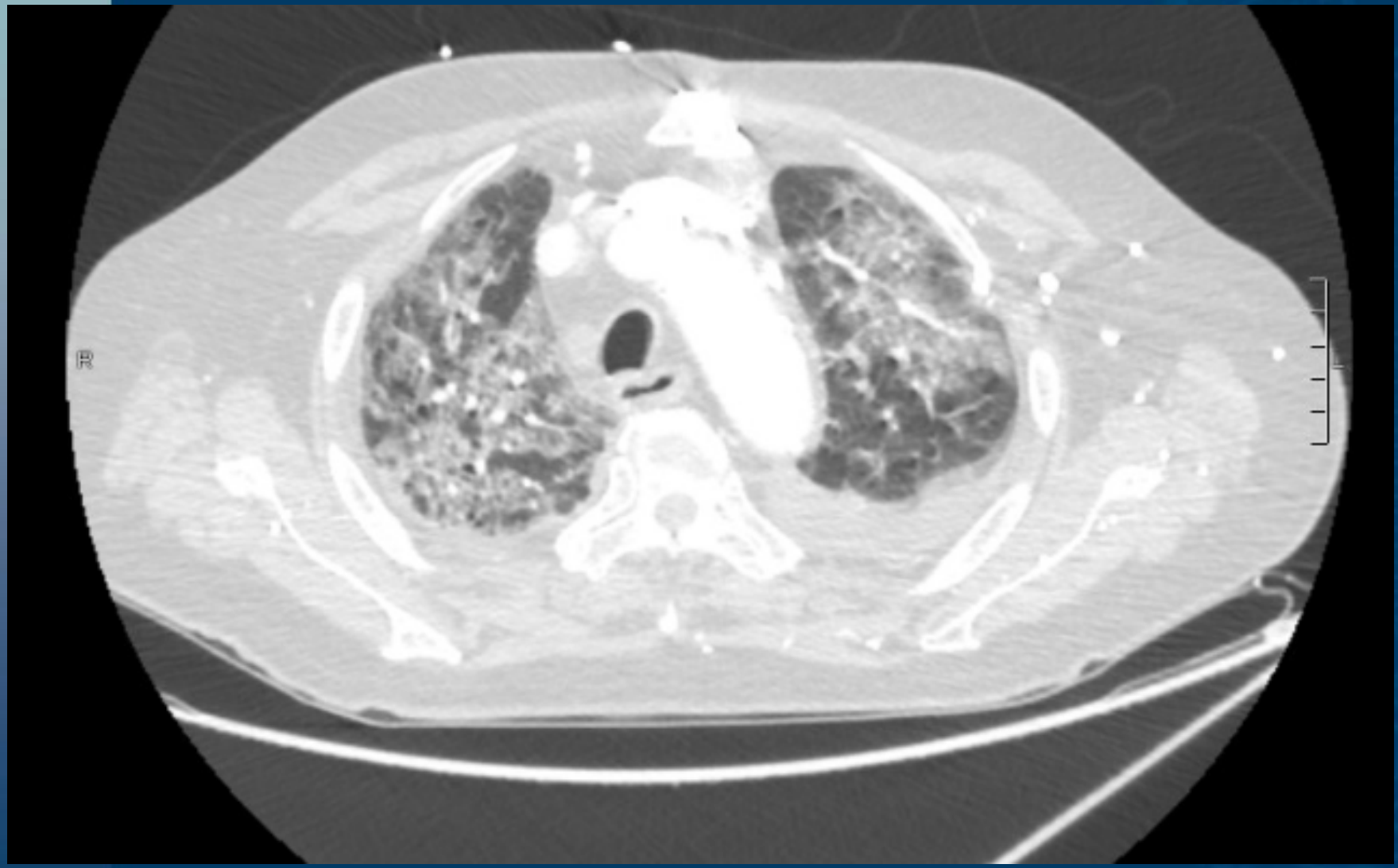

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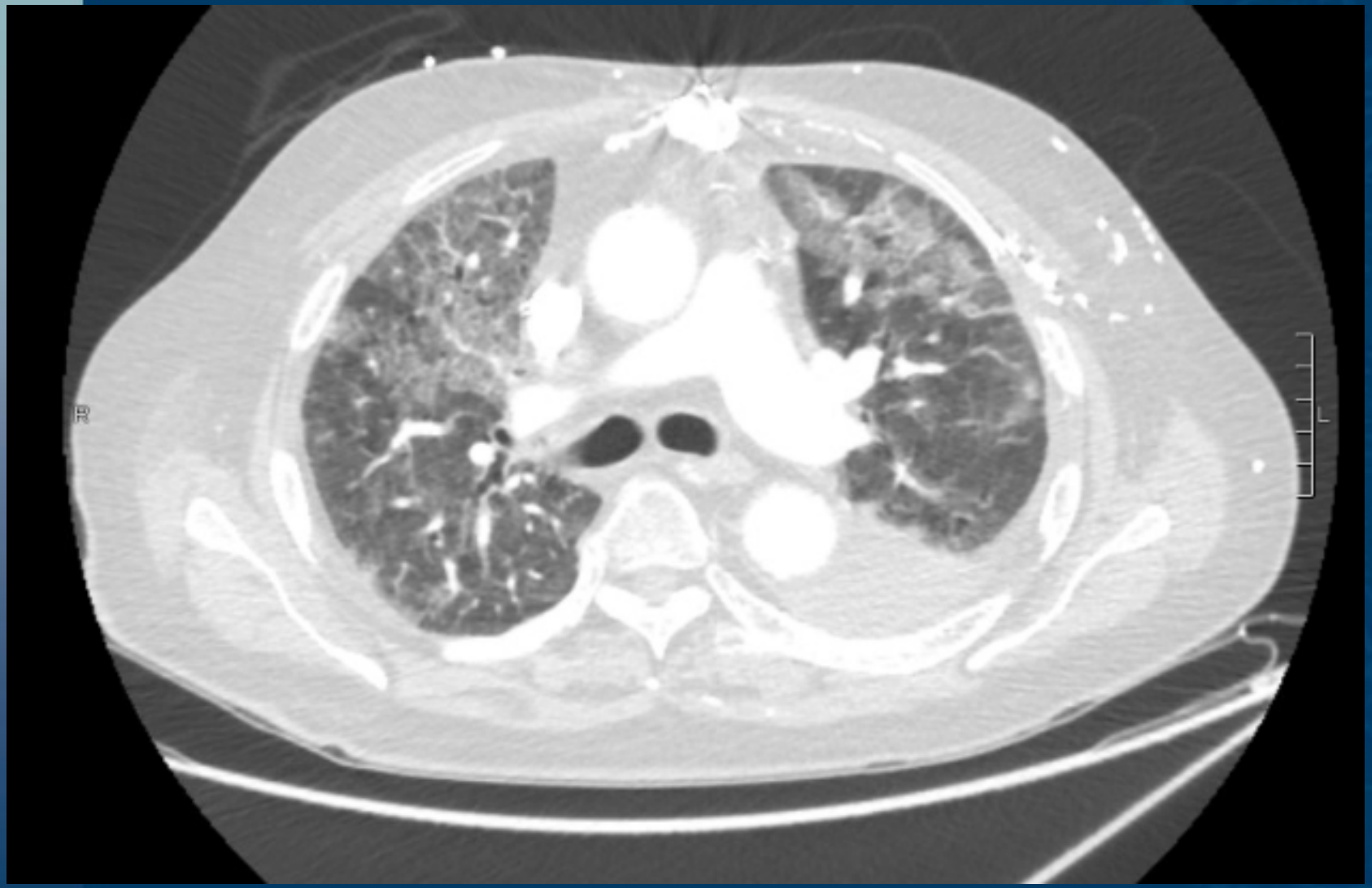

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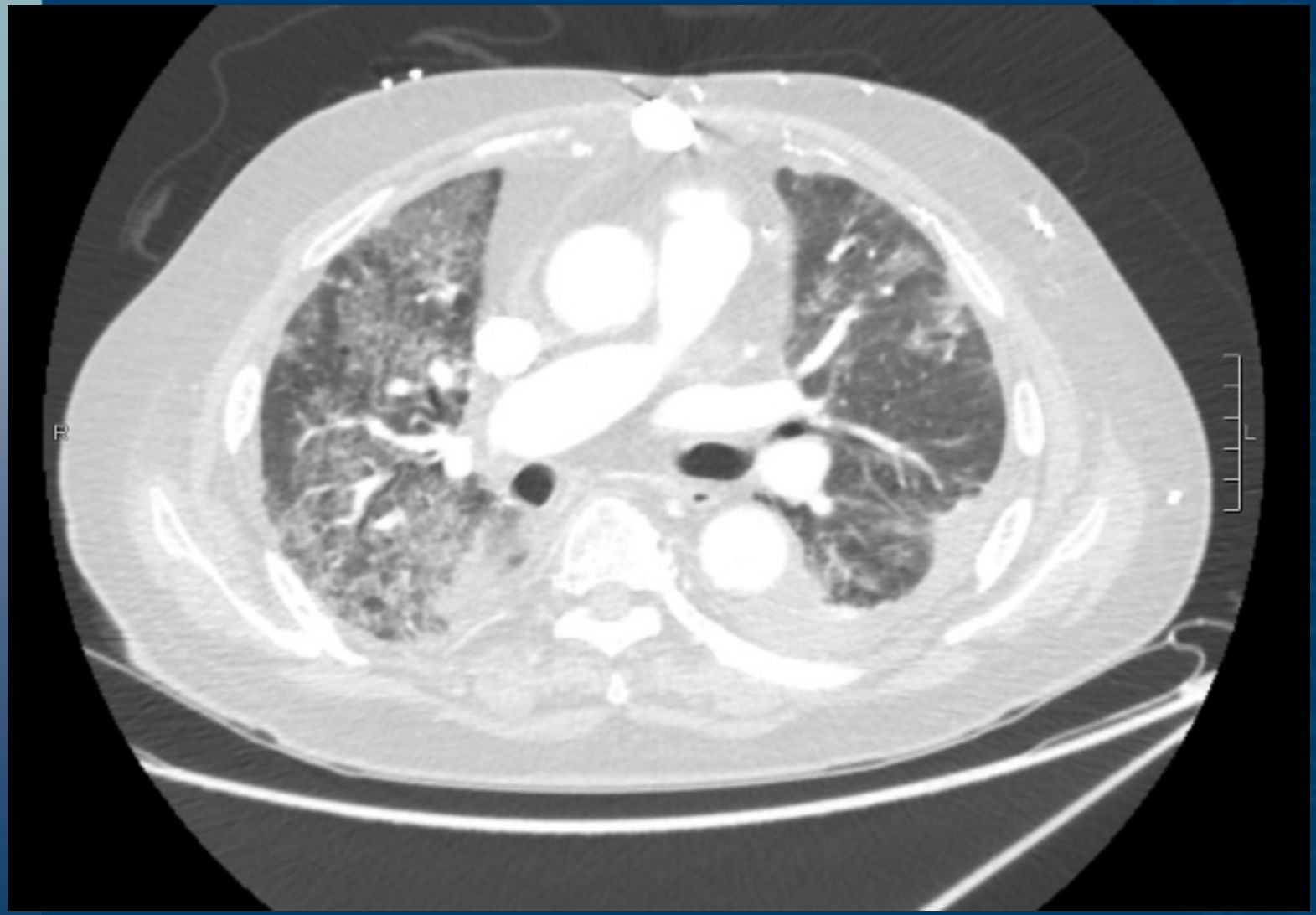

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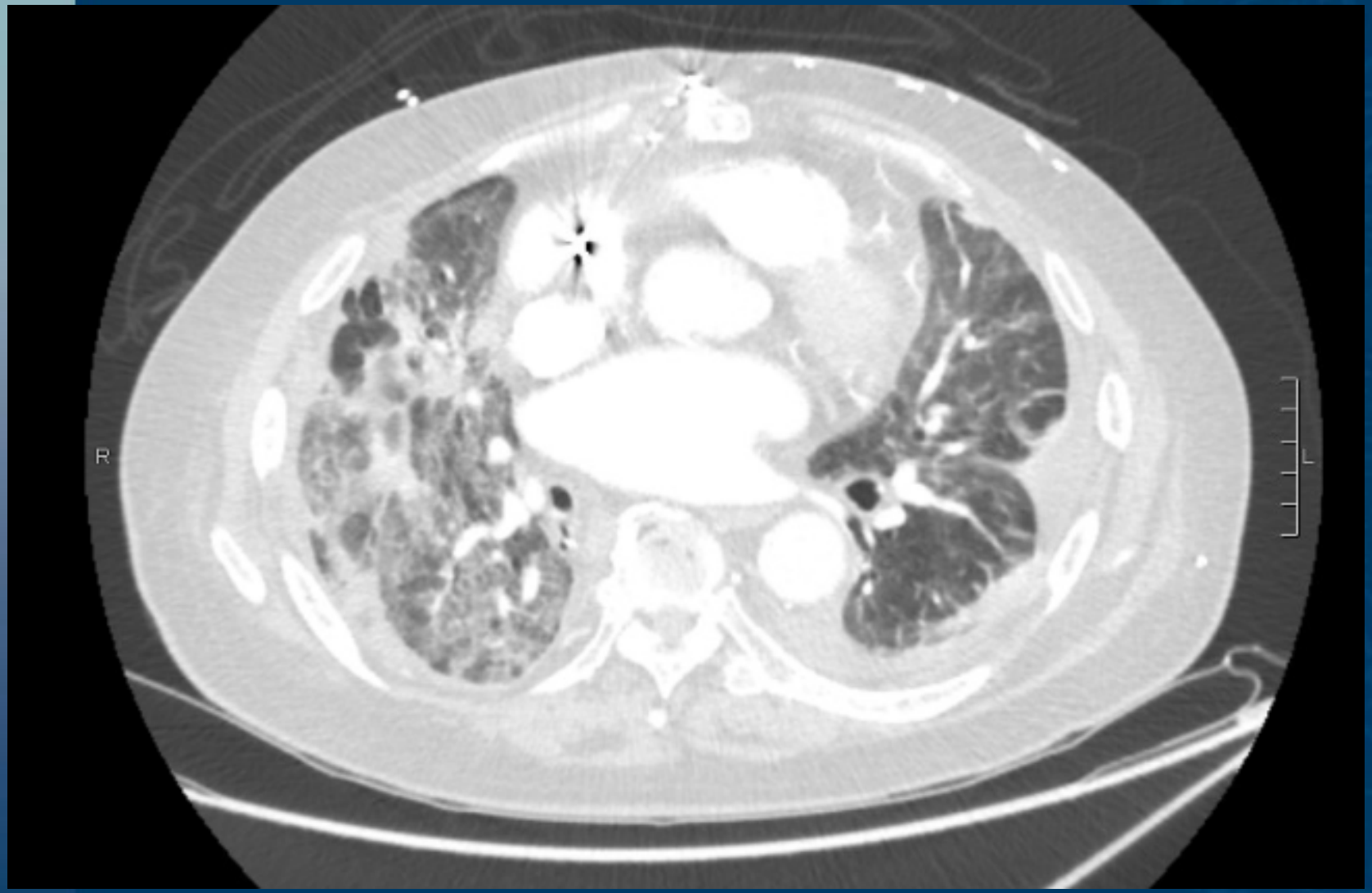

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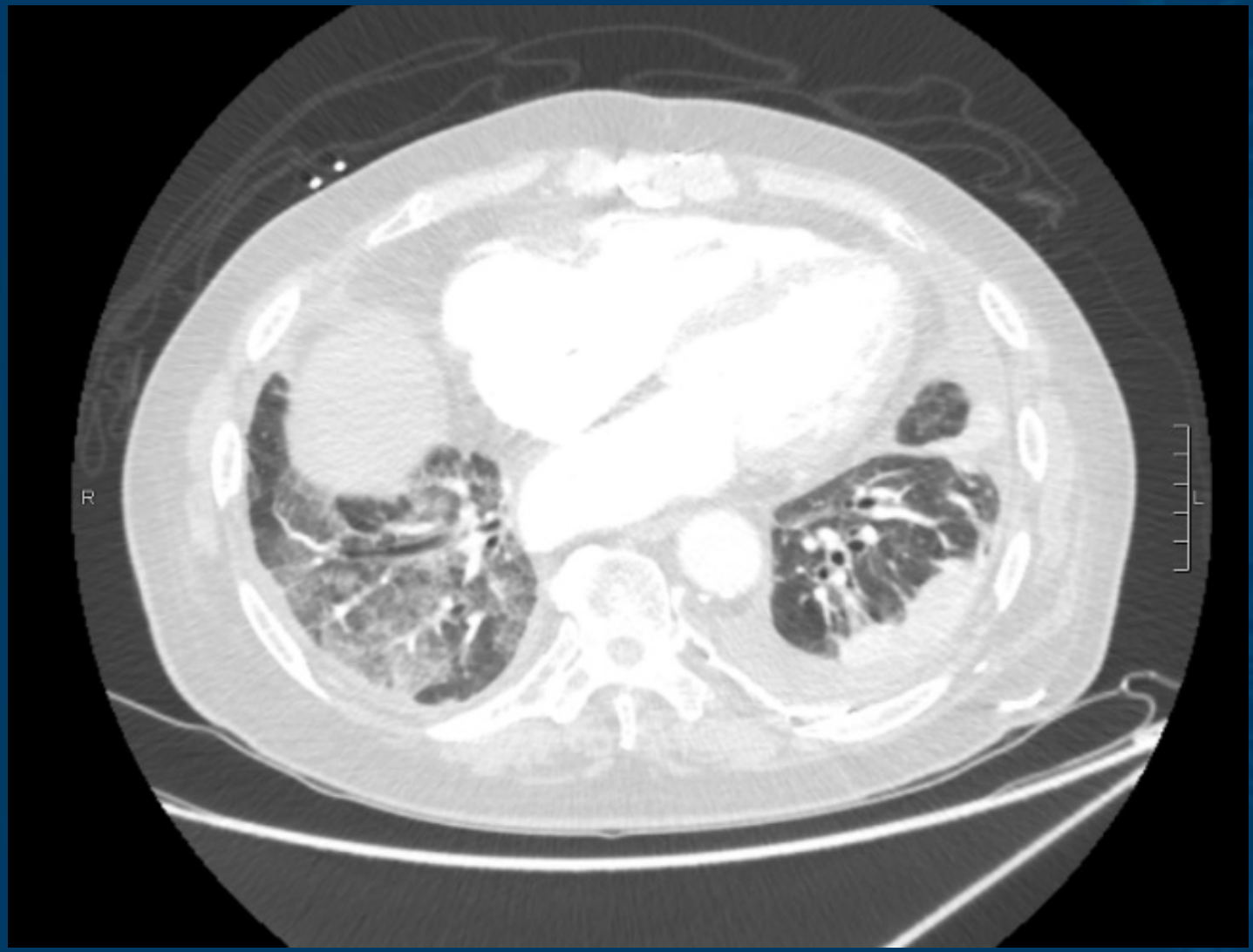


Special thanks to Shoshana Zha, MD for case / slides

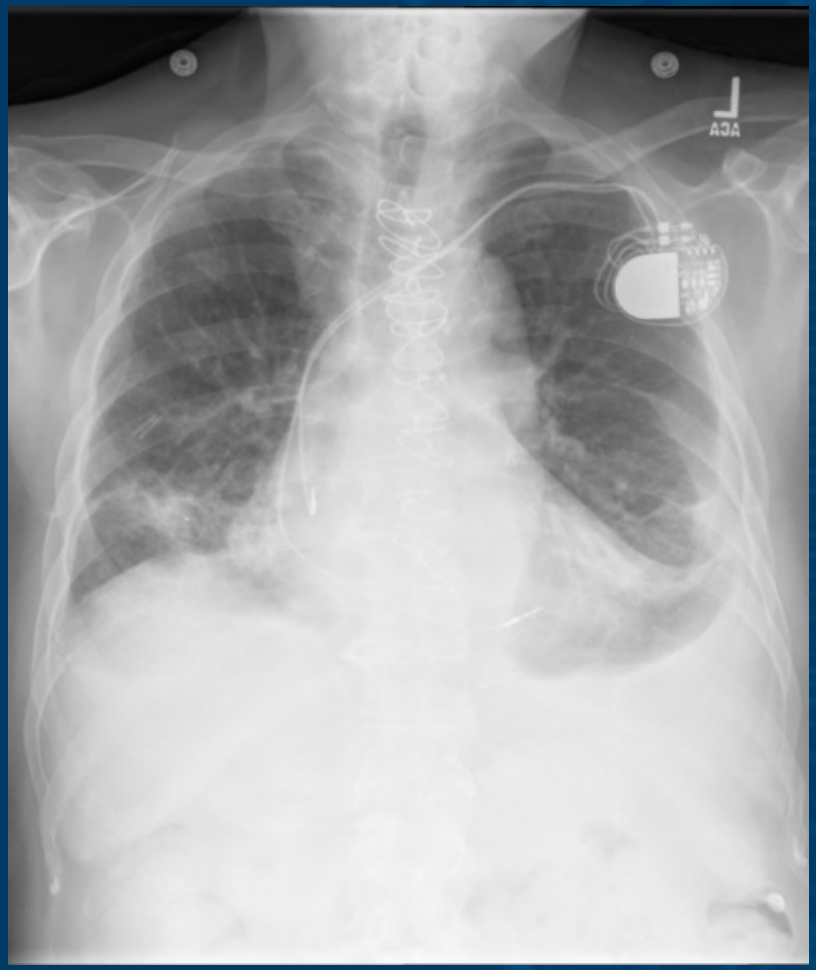
Case 3 -progression

- Day after admission, O2 titrated up to 10-12LPM
- On review with wife, prednisone had been discontinued

Special thanks to Shoshana Zha, MD for case / slides

Case 3 - improvement

- Started on prednisone 40mg/day and down to 2LPM within 4 days
- Discharged to take 20mg/day x 2 weeks, then 15mg/day until follow-up



Special thanks to Shoshana Zha, MD for case / slides

Radiation induced lung injury

Radiation Pneumonitis	Radiation Induced Organizing Pneumonia	Radiation Induced Fibrosis
o < 6 months o Dry cough o Progressive dyspnea o Low-grade fevers or chills o Malaise o Pleuritic chest pain o Immediately capillary leakiness, delayed exudative alveolitis	o 3 – 6 months o Dry cough o Progressive dyspnea o Low-grade fevers or chills o Malaise o More diffuse disease o Priming of lymphocytes	o >6 months o May be asymptomatic o High chronic inflammation → circulating platelet-derived and basic fibroblast growth factor

Murray et al, 2012. Radiation oncology, 7123
Ding et al. 2013 Curr drug targets. 14, 1247-1356
Giridhar et al, 2015. Asian Pac J Cancer Prev, 16(7), 2613-2617

Imaging and Radiological grading scale (RTOG)

Radiation Pneumonitis

- I – GGO without fuzziness of subjacent pulmonary vessels
- II – GGO extending beyond radiation field or consolidations
- III – focal consolidation +/- elements of fibrosis
- IV – dense consolidation, traction bronchiectasis, volume loss

Radiation-induced organizing pneumonia

- Outside radiation field → Often more pronounced in contralateral lung
- Migrates
- Relapses

Oie et al, 2013. Radiation Oncology. 856
Kouloulias et al 2014, Asian Pacific J Cncer Prev, 14 2717-22
Murai et al, 2012. Radiatin Oncology 7:123

Risk/Associated factors

- Smoking History
- Age >65
- Underlying lung disease
- Tumor location: mid-lower lung
- Adjuvant chemotherapy
- Risk with stereotatic (SBRT) 5-10% (up to 28% in older trials)
  - Often lower grade disease
  - Risk stage III with larger tumor
- Expression of Krebs Von den lungen-6

Ochiai et al, 2015. J Radiat Res. 56 (6): 904-11
Yamashita et al, 2014. World J Radiol. 6(9):708-15

Corticosteroids

- Mainstay of therapy since 1950s
- No standard, but initial dose often Prednisone 0.5 – 1 mg/kg
- High risk of relapse, thus slow / prolonged taper is important
  - Literature dating back to 1960s note relapse with rapid withdrawal of steroids
  - Textbooks recommend decrease of 10mg q2weeks – no trials/data of support this recommendation

Otani et al, 2014. Cancer Medicine, 3(4): 947-953

Experimental approaches

- Pentoxyphylline – reduced fibrosis in rats (sterreicher et al 2001)
- Prophylactic anti-inflammatories
- Inhaled steroids
- Case reports of azathioprine and cyclosporine

Hekenberens et al, 2016. Radiation Oncology 11:12

Radiation induced lung injury summary

- Important to try to differentiate ***Radiation Pneumonitis*** from ***Radiation Induced Organizing Pneumonia***

- If significantly hypoxic, consider steroids but ***TAPER VERY SLOWLY***

Take Home Points

- A single drug can be associated with multiple lung injury patterns
  - Variety of histologic and radiographic patterns
  - Histologic patterns don't correlate well with imaging findings

- In most situations, must rely on
  - **temporal relationship** between the administration of drug and the onset of lung injury,
  - along with the exclusion of other potential causes, particularly infections and metastatic disease

Take Home Points

- Grade the degree of lung injury to determine the next steps in therapy / management

- If has also received XRT or SBRT, consider Radiation induced lung injury patterns:
  - ***Radiation Pneumonitis***
  - ***Radiation Induced Organizing Pneumonia***
  - ***Radiation Induced Fibrosis***