Drug-Induced - Iatrogenic Respiratory Disease

- Department of Pulmonary Medicine, Thoracic Oncology and Intensive Care

- Dijon - France
- www.pneumotox.com

- Athens Dec 2019

Dijon

- C.O.I.: *nihil*

Magnitude of the Problem

- 1973: John L Stauffer: 120 drugs/769 papers

Medical Staff Conference

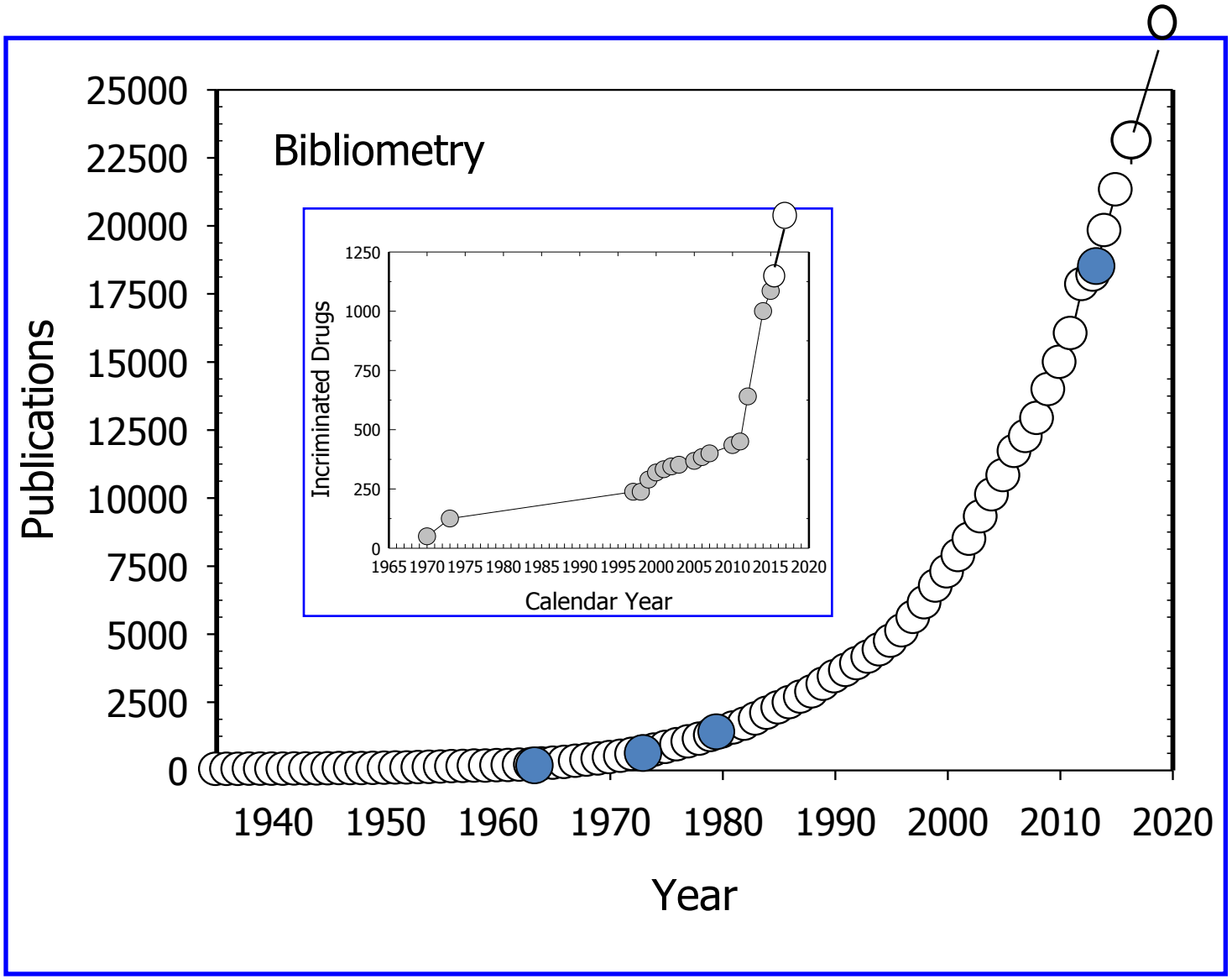
Refer to: Drug-induced lung disease: The price of progress—Medical Staff Conference, University of California, San Francisco. Calif Med 119:48-55, Oct 1973

Drug-Induced Lung Disease:

The Price of Progress

1,519 drugs/agents/procedures - 602 patterns

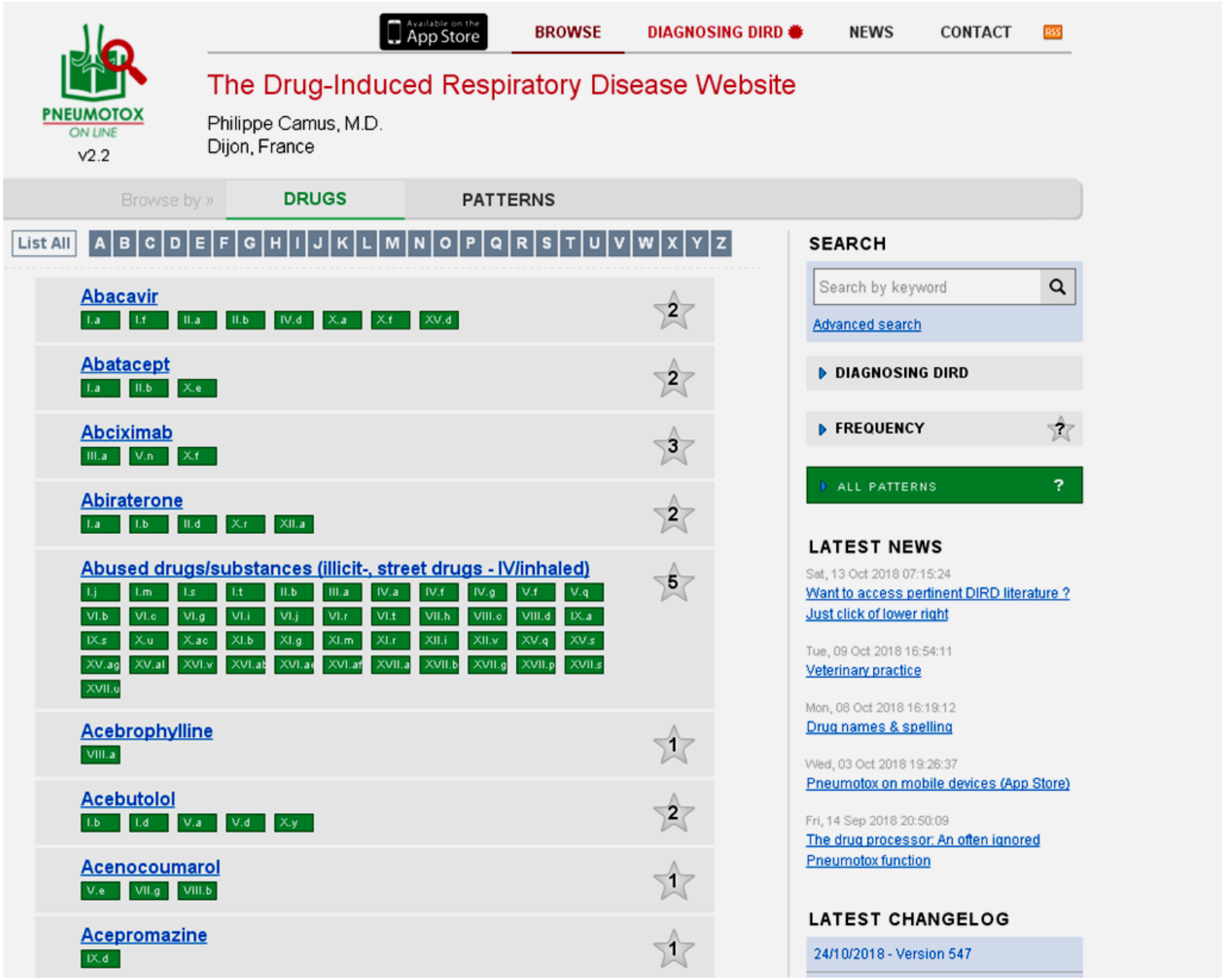
28777 (35.000) papers

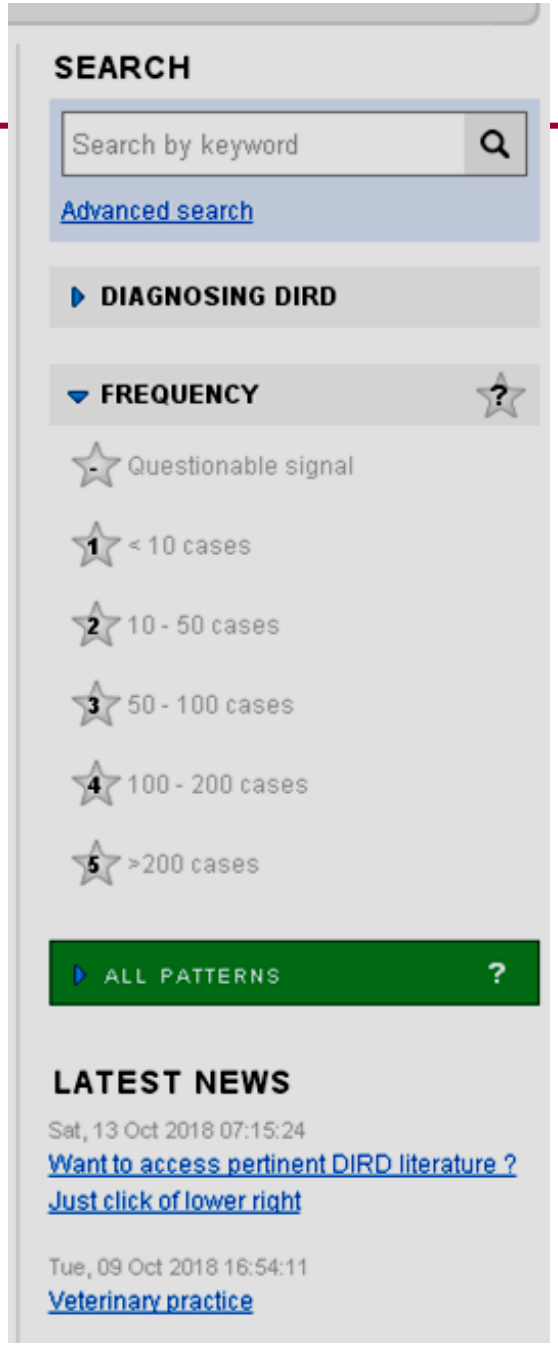


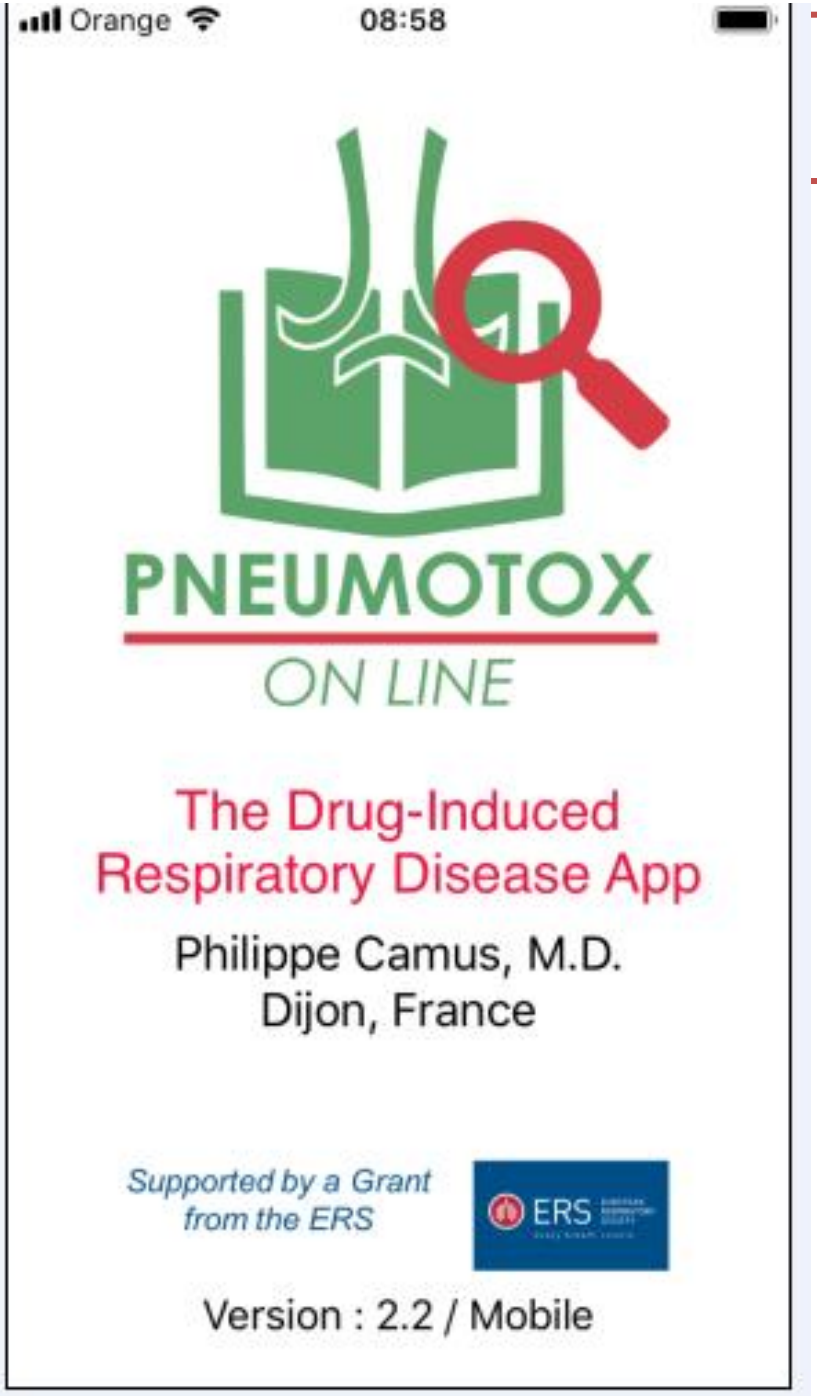
Last 3 days…

- Arnaud, L., et al., ***Drug-induced systemic lupus****: revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database.* Ann Rheum Dis, 2019. 78: 504-8.
- Timlin, H., et al., *Clinical Characteristics of* ***Hydralazine-induced Lupus****.* Cureus, 2019. 11: e4996
- Raschi, E., et al., ***Drug-induced systemic lupus erythematosus: should immune checkpoint inhibitors be added to the evolving list****?* Ann Rheum Dis, 2019
- Irani, M., et al., ***Unilateral pleural effusion*** *as the sole clinical presentation of severe ovarian hyperstimulation syndrome: a systematic review.* Gynecol Endocrinol, 2018. 34: 92-9.
- Kariisa, M., et al., ***Drug Overdose Deaths*** *Involving Cocaine and Psychostimulants with Abuse Potential - United States, 2003-2017.* MMWR Morb Mortal Wkly Rep, 2019. 68: p. 388-95.
- Seth, P., et al., ***Overdose Deaths*** *Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016.* MMWR Morb Mortal Wkly Rep, 2018. 67: 349-58.
- Deng, Y., et al., *Clinical Management of Risk of* ***Radiation Pneumonia*** *with Serum Markers During the Radiotherapy for Patients with Thoracic Malignant Tumors.* Cancer Manag Res, 2019. 11:. 10249-56
- Hallowell, R.W., et al., ***Case 38-2019****: A 20-Year-Old Man with Dyspnea and Abnormalities on Chest Imaging.* N Engl J Med, 2019. 381: 2353-63

Pneumotox 1997

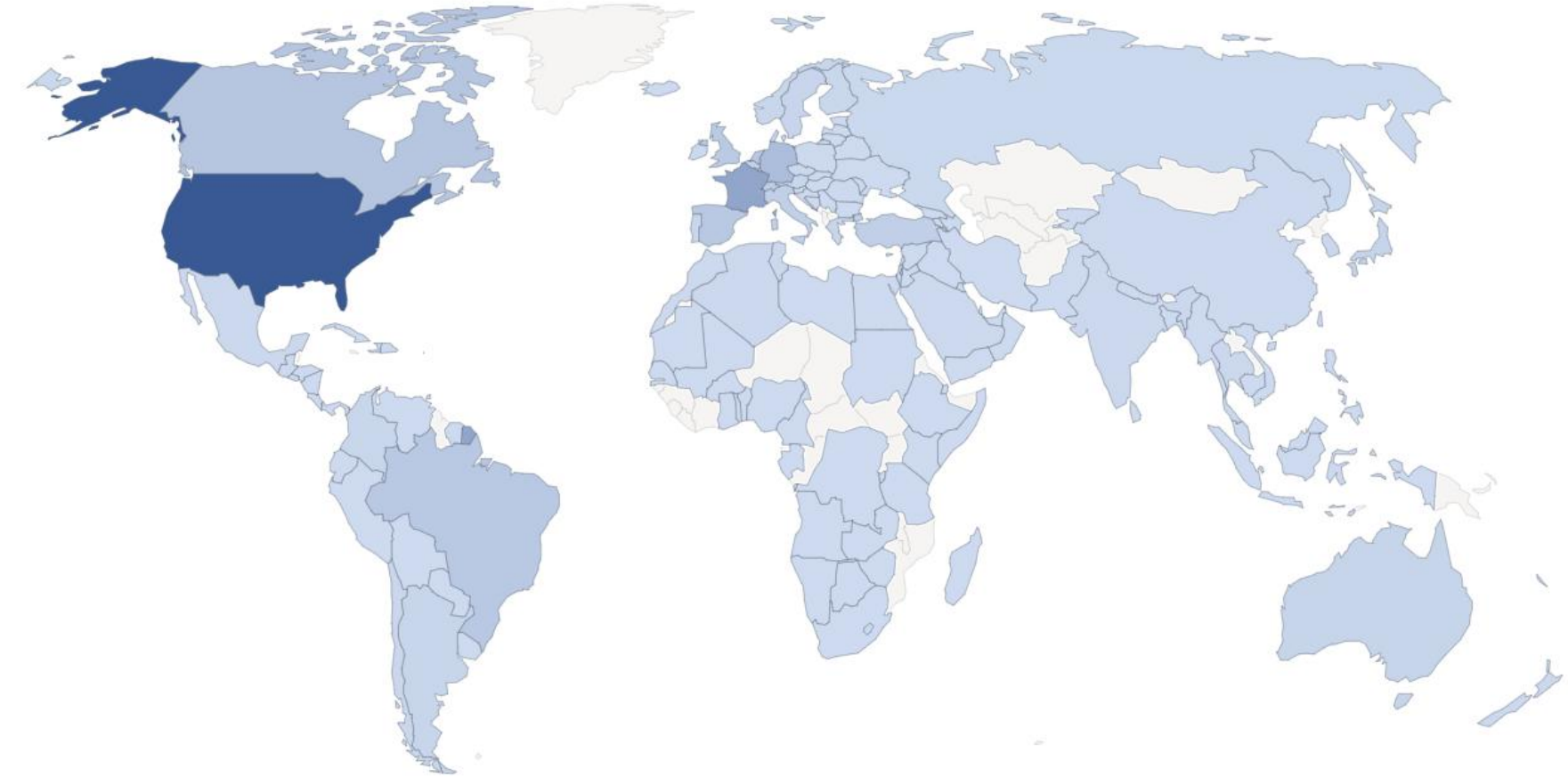



SEARCH
Search by keyword
Advanced search
DIAGNOSING DIRD
FREQUENCY
?
- Questionable signal
1 < 10 cases
2 10 - 50 cases
3 50 - 100 cases
4 100 - 200 cases
5 >200 cases
ALL PATTERNS
?
LATEST NEWS
Sat, 13 Oct 2018 07:15:24
Want to access pertinent DIRD literature ?
Just click of lower right
Tue, 09 Oct 2018 16:54:11
Veterinary practice


Orange
08:58
PNEUMOTOX
ON LINE
The Drug-Induced
Respiratory Disease App
Philippe Camus, M.D.
Dijon, France
Supported by a Grant
from the ERS
ERS
Version : 2.2 / Mobile

Visitor Map

110,767 visits



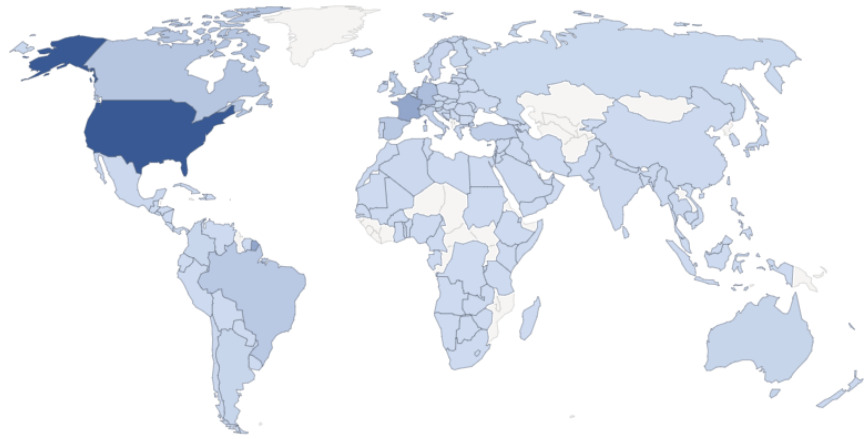
Countries Cities

World-Wide

Visits

WWW.PNEUMOTOX.COM | FROM 2018-08-10 TO 2019-12-12 | ALL VISITS | NEW UPDATE: MATOMO 3.13.0

110,767 visits

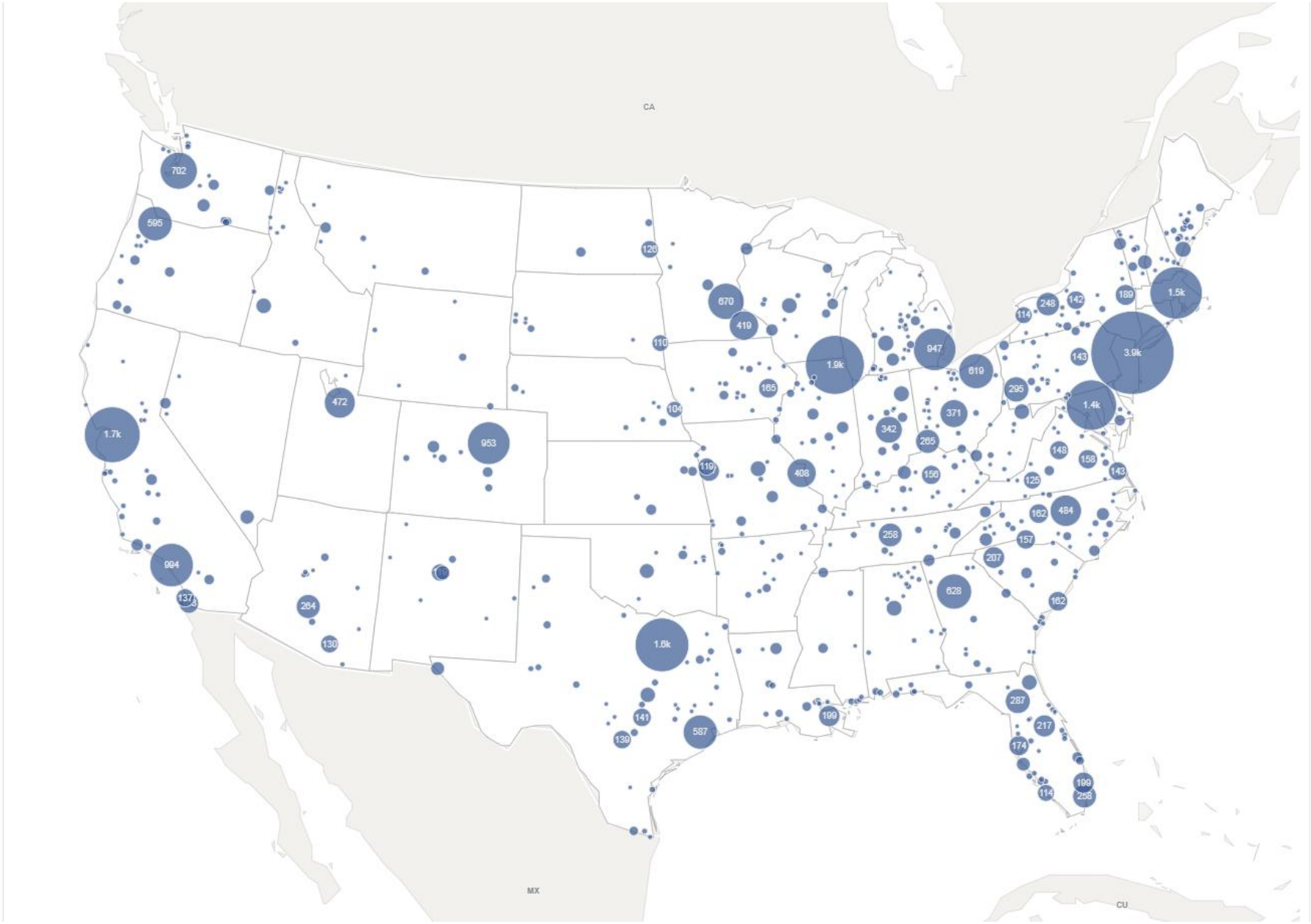


Continent

CONTINENT	VISITS
Europe	52,854
North America	41,674
South America	7,654
Asia	5,302
Oceania	1,666
Africa	1,345

Country

COUNTRY	VISITS
United States	35,927
France	13,880
Germany	7,331
Canada	5,337
Brazil	4,680
Netherlands	4,573
Spain	4,457
United Kingdom	4,101
Switzerland	3,193
Turkey	2,659
Italy	2,407
Belgium	1,787
Australia	1,354
Japan	1,342
Sweden	1,192
Argentina	1,122
Greece	990
Denmark	961
Portugal	947
Colombia	855
Norway	840
South Korea	744


CA
MX
CU
702
595
472
1.7k
953
994
137
264
130
126
670
419
110
1.9k
185
104
119
408
1.6k
141
139
587
199
947
619
342
371
265
156
295
1.4k
3.9k
1.5k
189
248
142
114
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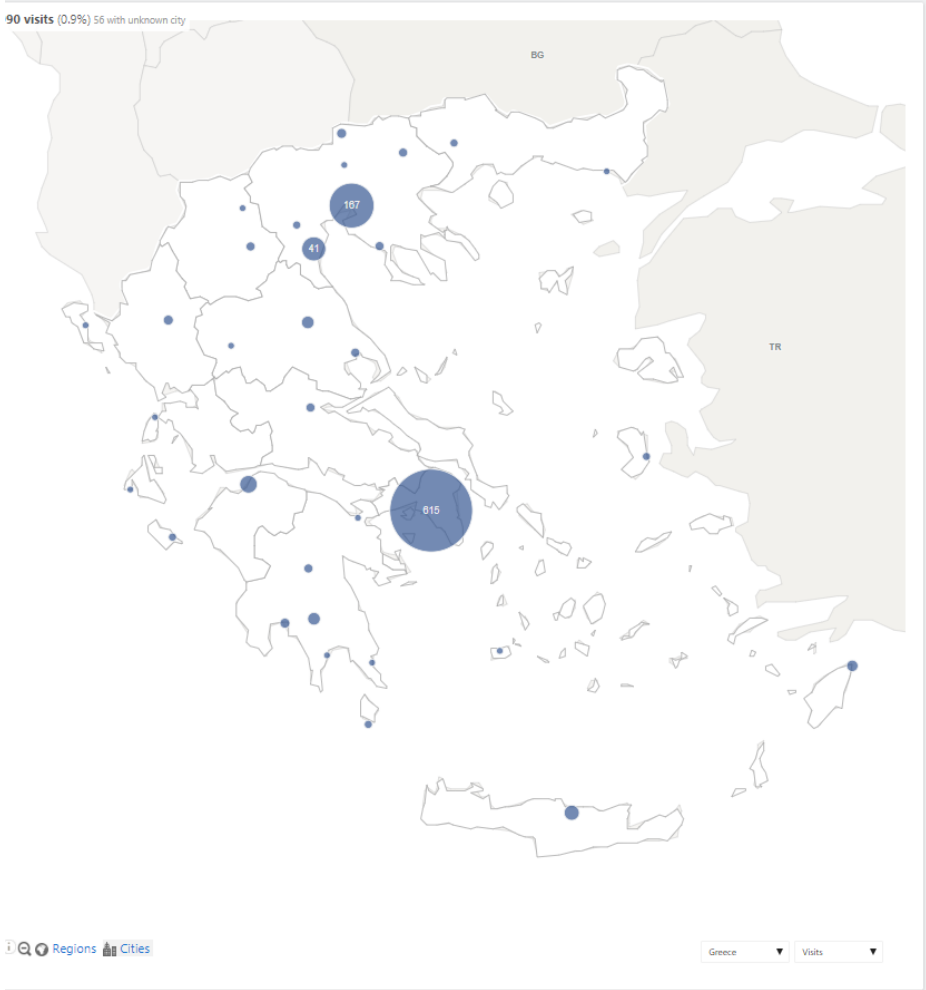


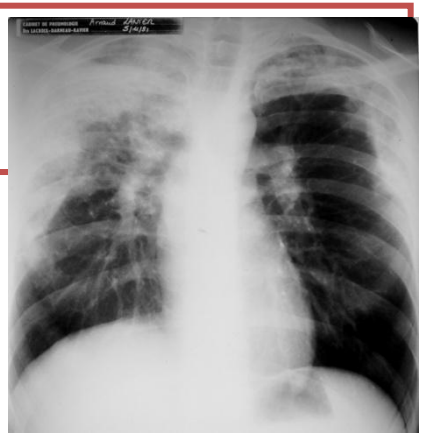
Country

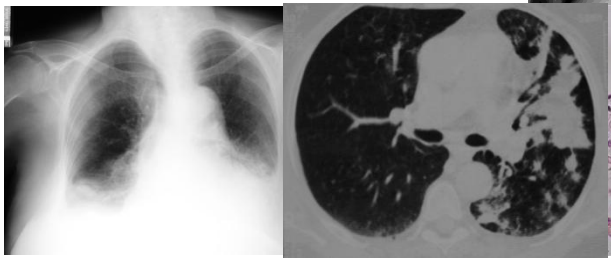
COUNTRY ▲	VISITS
Algeria	402
Andorra	5
Angola	1
Argentina	1,122
Armenia	1
Australia	1,354
Austria	611
Azerbaijan	5
Bahrain	42
Bangladesh	3
Belarus	1
Belgium	1,787
Benin	7
Bolivia	2
Bosnia & Herzegovina	6
Botswana	2
Brazil	4,680
Bulgaria	56
Burkina Faso	3
Burundi	1
Cambodia	15
Cameroon	1
Canada	5,337
Cape Verde	2
Chile	737
China	243

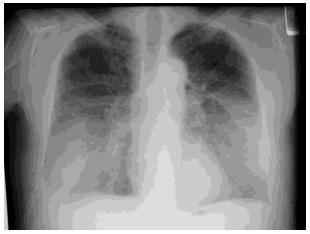

Mer Noire
Skopje
BULGARIE
Kirklareli
Zonguldak
Durrës
Peshkopi
Edirne
Lüleburgaz
ALBANIE
Komotiní
Çorlu
İstanbul
Fier
Pogradec
Sérrai
Tekirdağ
Vlorë
Kaválla
İzmit
Adapazarı
Korçë
Thessalonique
Bandırma
Bursa
Katerini
Karacabey
Sarandë
Çanakkale
Eskişehir
Ioánnina
Larissa
Edremit
Balıkesir
Corfou
Vólos
Kütahya
Trikala
Soma
Mytilène
KÜTAHYA
Árta
Lamía
Afyon
Agrínion
Akhisar
Delphi
Uşak
Mer Ionienne
Patras
Aíyion
Turgutlu
Kitheronas
İzmir
Denizli
İsparta
Pírgos
Athènes
Söke
Aydın
Tripolis
Muğla
TURQUIE
GRÈCE
ÎLES DE LA
Kalamáta
Guythion
MUĞLA
Antalya
MER ÉGÉE
Alanya
Rhodes
Mer Égée
La Canée
Héraklion
Mer Méditerranée

By 1960 (n:198)–Mostly solo

- Aspirin-induced:
  - Pulmonary edema
  - Catastrophic bronchospasm
- p-aminosalicylate eosinophilic pneumonia
- Radiation-induced lung injury
- Exogenous lipoid pneumonia
- Hydralazine-induced *lupus*







1960s

Pleuropulmonary Reaction to Nitrofurantoin

Benjamin R. Robinson, MD, Woodland, Calif

NITROFURANTOIN is frequently used for short and long term treatment of urinary tract infections. As with many drugs, various types of allergic or toxic reactions have occurred, the most serious of which is anaphylactic shock.[1]

An unusual reaction to nitrofurantoin consisting of pulmonary infiltration and pleural effusion was reported by Israel and Diamond in May, 1962.[2] Three other reports have appeared in the foreign literature.[3-5]

Because of its rarity of occurrence, but alarming picture that it may present, this case is presented.

CHRONIC NITROFURANTOIN PULMONARY REACTION*

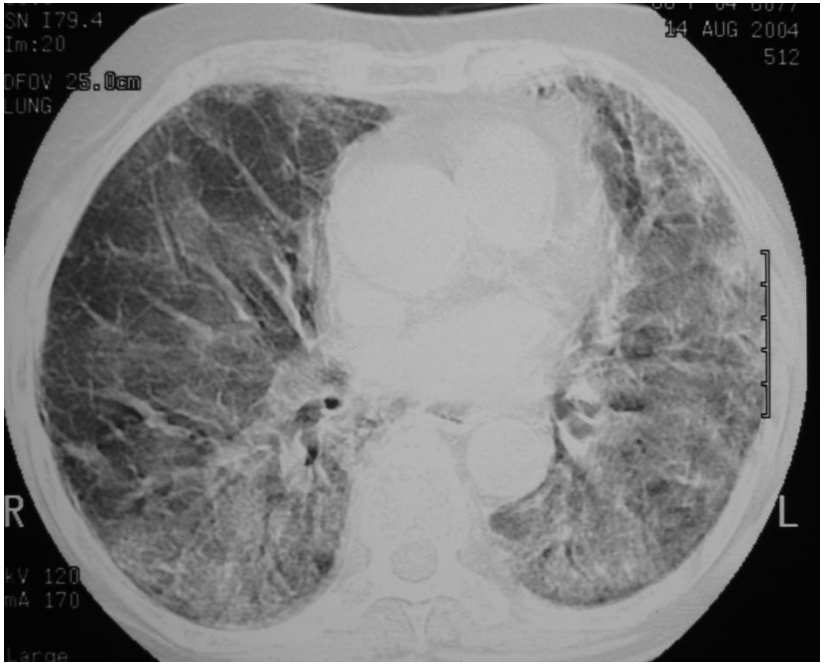
Report of Five Cases

E. C. Rosenow, III, M.D., Richard A. DeRemee, M.D., and David E. Dines, M.D.

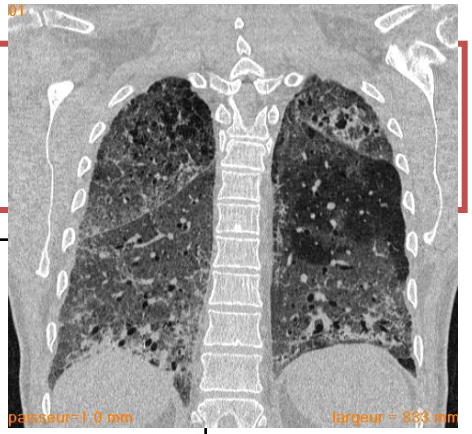
Abstract In five cases diffuse interstitial pneumonitis or fibrosis, or both (as proved by lung biopsy), was seen after long-term therapy with nitrofurantoin. The acute form of nitrofurantoin pneumonitis is characterized by the sudden onset of cough, dyspnea and fever, and the rapid disappearance of the symptoms and findings when the use of the drug is discontinued. The chronic form is insidious in onset, is not associated with a febrile reaction, produces a nonspecific histologic and radiologic picture of diffuse interstitial pneumonitis or fibrosis, or both, and may be at least partially reversible when the drug therapy is discontinued and steroids are employed.

1960s: Nitrofurantoin

- Acute
- <2w] into Rx
- SOB, cough, chest pain, fever
- Minimal pleural effusions
- Mod^{te} blood eosinophilia
- Withhold the drug
- W/wo corticosteroids



Nitrofurantoin, subacute-chronic



ORIGINAL ARTICLE

Chronic Nitrofurantoin–Induced Lung Disease

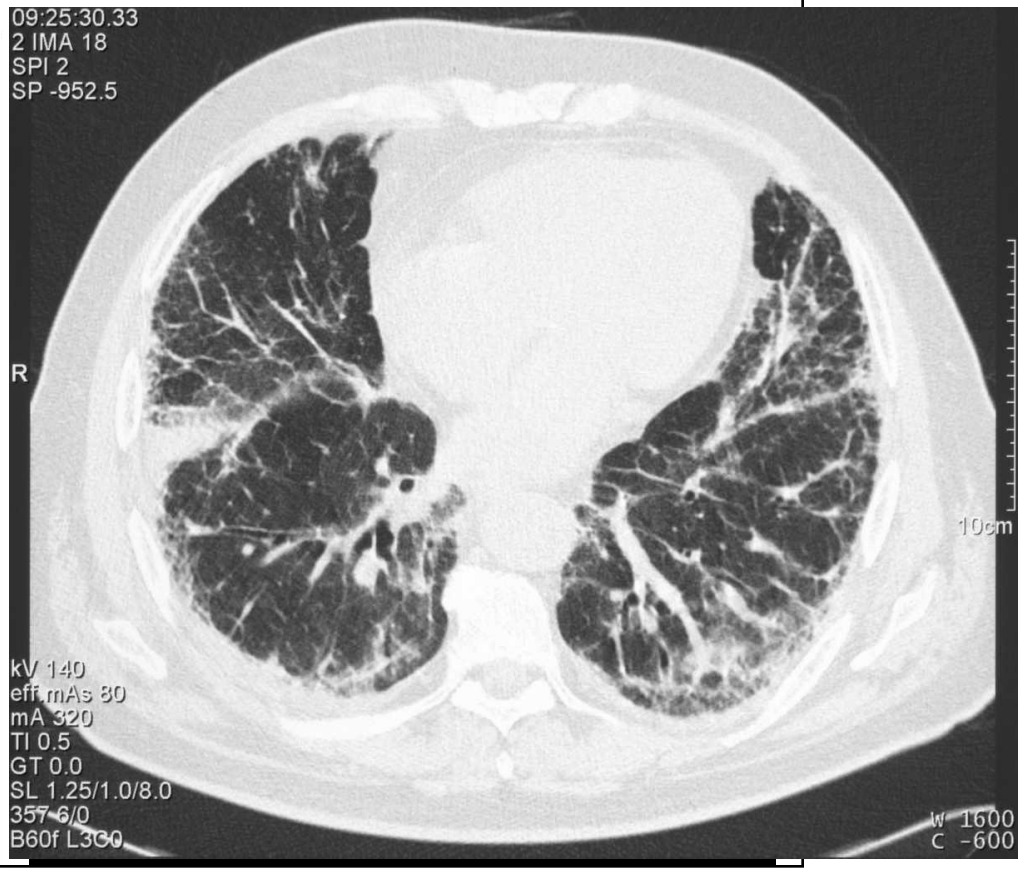
JOSE L. MENDEZ, MD; HASSAN F. NADROUS, MD; THOMAS E. HARTMAN, MD; AND JAY H. RYU, MD

OBJECTIVE: **To reassess the clinical and radiological features of chronic nitrofurantoin–induced lung disease and eventual clinical outcome.**

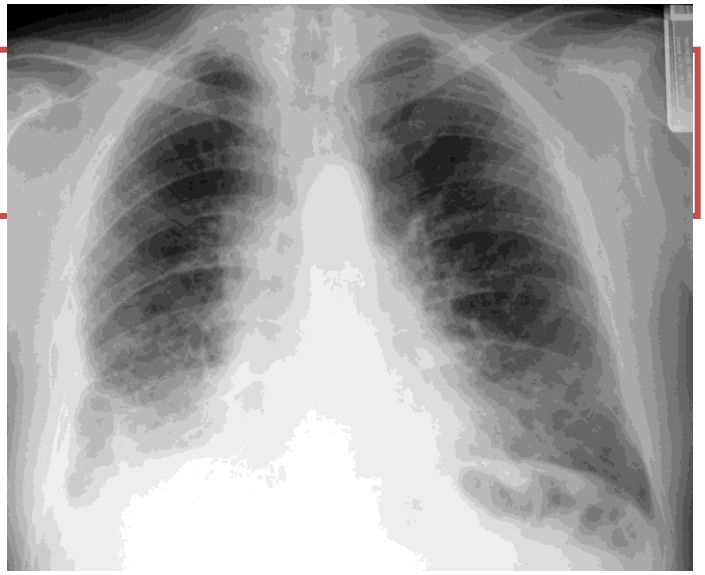
PATIENTS AND METHODS: **We retrospectively reviewed the medical records of 18 patients with chronic nitrofurantoin–induced lung disease who were seen at the Mayo Clinic in Rochester, Minn, from January 1, 1997, to December 31, 2002.**

RESULTS: **The median age of the 18 patients was 72 years (range, 47-90 years) at the time of diagnosis; 17 (94%) were women. Onset of symptoms occurred after a median interval of 23 months (range, 10-144 months) following the initiation of nitrofurantoin therapy for the prevention of recurrent urinary tract infections. All patients presented with persistent dyspnea and cough associated with lung infiltrates detected on chest radiography. Ten computed tomograms were available for review and revealed bilateral areas of ground-glass opacities in all cases and showed subpleural irregular linear opacities and patchy consolidation in some cases. Nitrofurantoin therapy was discontinued in all patients, and most improved subsequently; 9 patients received corticosteroid therapy.**

CONCLUSIONS: **Chronic nitrofurantoin–induced lung disease is seen predominantly in older women who present with respiratory symptoms after a year or more of nitrofurantoin therapy. Associated radiological features are relatively nonspecific but usually include bilateral areas of ground-glass opacities on computed tomography of the chest. Cessation of nitrofurantoin therapy leads to improvement and suffices in the management of some patients, although corticosteroid therapy may be helpful in those more severely affected.**



Mendez *et al*. 2005



- Idiopathic ILD mimic
- 18 patients 17 women
- Mean time of onset: 23 months
- Mean time to diagnosis: 4 months
- Eosinophilia: 17%
- Lung biopsy: NSIP, OP, giant cells
- Withdrawal: 18/18
- Steroids: 9/18
  - Improved: 16
  - Stable: 2
  - Residual disease: 12

Nitrofurantoin, chronic

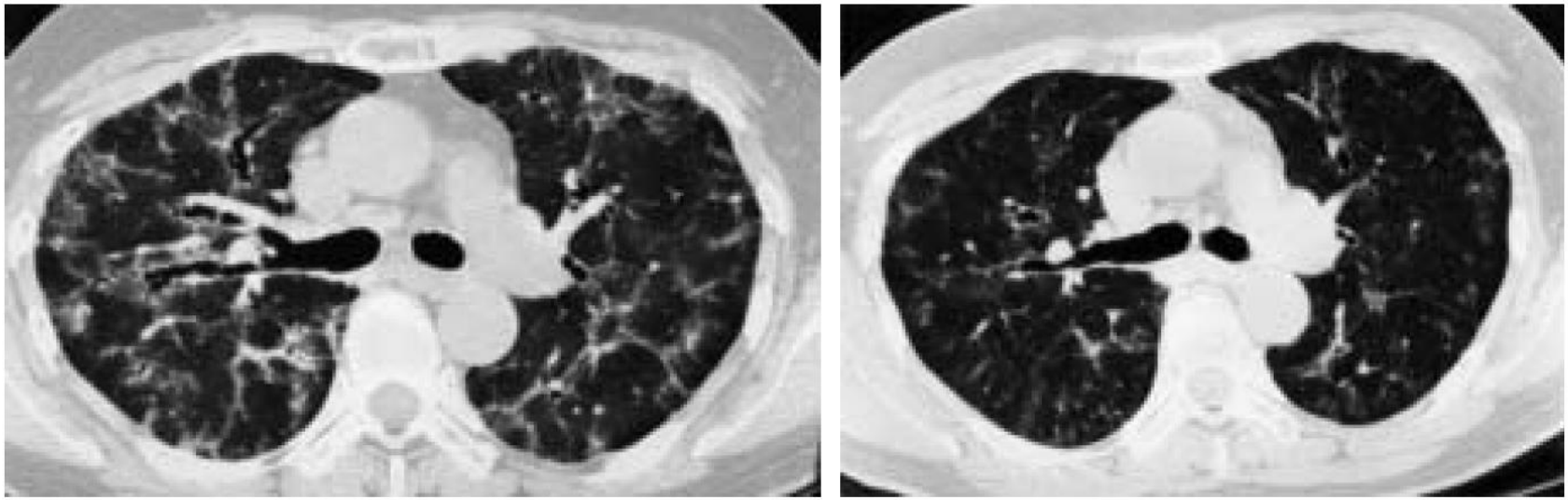


FIGURE 2. High-resolution computed tomograms of a 67-year-old woman with chronic nitrofurantoin–induced lung disease. This nonsmoker had been receiving nitrofurantoin therapy, 50 mg/d, for 7 years and had been symptomatic with exertional dyspnea and cough for the preceding 12 months. Left, Image at initial presentation shows scattered areas of ground-glass attenuation that are located in subpleural areas and along the bronchovascular bundles. Right, Image obtained 5 months after cessation of nitrofurantoin therapy (no corticosteroid therapy) reveals substantial improvement in the parenchymal infiltrates.

BMJ

BMJ 2013;346:f3897 doi: 10.1136/bmj.f3897 (Published 18 June 2013)

LETTERS

RECURRENT UTI IN NON-PREGNANT WOMEN

Is "nitrofurantoin lung"on the increase?

Adam D L Marshall *respiratory registrar*, Owen J Dempsey *consultant chest physician*

Chest Clinic C, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, UK

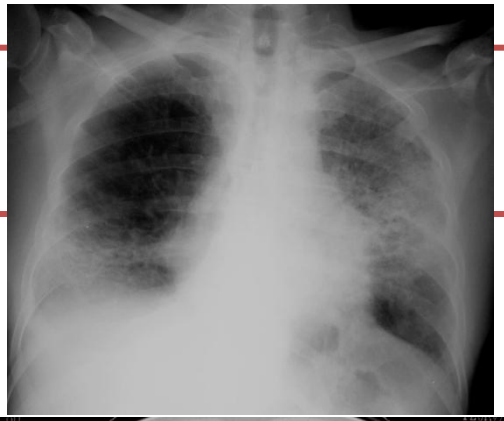
Fatal Nitrofurantoin Lung

Jai B Mullerpattan*, Rucha S Dagaonkar**, Hardik D Shah**, Zarir F Udwadia***

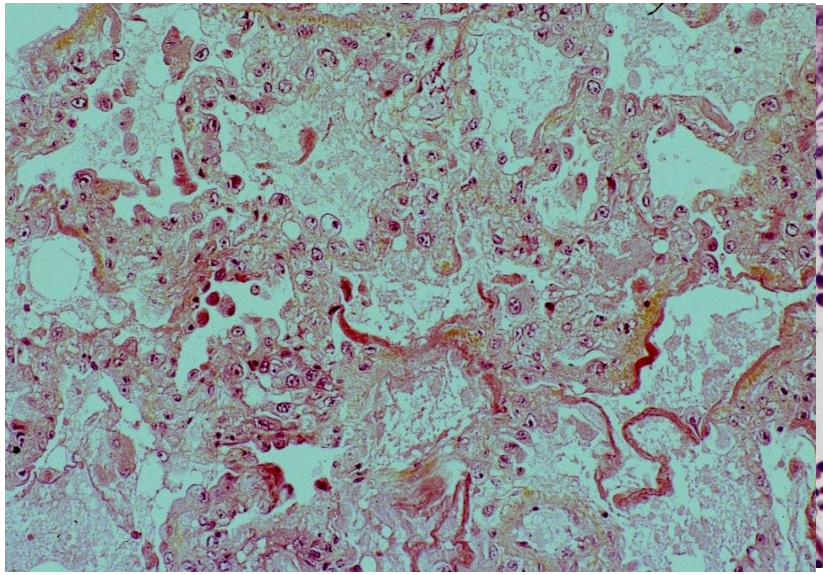
Abstract

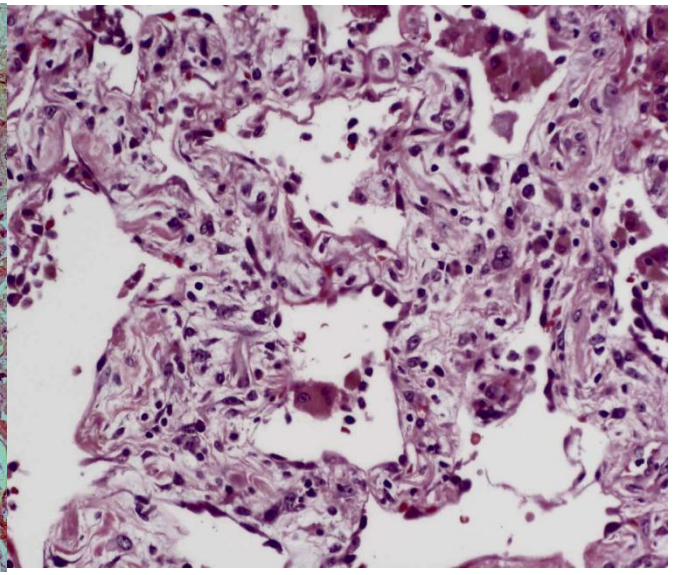
Nitrofurantoin is a drug commonly used for urinary tract infections. It acts by damaging bacterial DNA. It is given in dose of 50-100 mg orally and is generally considered a safe drug but has occasionally been known to cause pulmonary toxicity which is usually reversible and only rarely fatal. We present a case of an elderly lady receiving nitrofurantoin for her urinary tract infection who developed sudden acute lung injury to which she finally succumbed within a few weeks.

60s ‘Chemotherapy lung’



- Bleomycin, busulfan chlorambucil, CPM melphalan, NUs
- <u>Early</u>:
  - PE, NSIP, DAD, ARDS





Chemotherapy-Associated Pulmonary Toxic Reactions During Treatment for Breast Cancer

Dorothy A. White, MD; Marilyn Orenstein, MD; Thomas A. Godwin, MD; Diane E. Stover, MD

• **Chemotherapy-related pneumonitis developed in eight patients during treatment for breast cancer. Six were receiving adjuvant therapy and two were being treated for metastatic disease. Fever, chills, dyspnea, and dry cough were the initial symptoms. Observations from chest roentgenograms varied from normal to bilateral interstitial-alveolar infiltrates. Results of pulmonary function tests were markedly abnormal, with a decreased diffusing capacity being the most characteristic abnormality. The pneumonitis developed in six patients while receiving 20 mg or less per day of prednisone and appeared temporarily related to tapering of steroid therapy in four patients. All patients recovered clinically, although prednisone therapy of 60 mg/day or its equivalent was required in three cases. Mild pulmonary function abnormalities persisted. Drug-induced pneumonitis should be considered in the differential diagnoses of patients with breast cancer in whom unexplained fever, dyspnea, or infiltrates develop during multidrug chemotherapy.**

(*Arch Intern Med* 1984;144:953-956)

The average age of the patients was 48 years (range, 32 to 68 years). The diagnosis of breast cancer had been confirmed histologically at Memorial Hospital, New York. Four were estrogen receptor positive and one had had a bilateral oophorectomy. No patient had had an adrenalectomy. Six patients were receiving adjuvant chemotherapy and two were receiving therapy for metastatic disease. Chemotherapy included methotrexate, fluorouracil, vincristine sulfate, and prednisone in all cases. In addition, cyclophosphamide was given except in patients 1 and 3 who received chlorambucil. Alkylating agents were taken orally daily and methotrexate was given intravenously in weekly doses. Four patients had a notable history of smoking and two of these had moderately severe obstructive lung disease.

Chest roentgenograms were performed in all eight patients. Lung function tests that included spirometry, lung volumes, and single-breath diffusing capacity were performed in seven of the eight patients. Spirometry was performed using standard spirometric techniques. Volumes were determined by the closed circuit helium dilution method.[5] The single-breath diffusing capacity for carbon monoxide was determined by the method of Ogilvie et al.[6] All values for diffusing capacity for carbon monoxide were corrected for hemoglobin concentration by applying the correc-

White *et al*. 1984

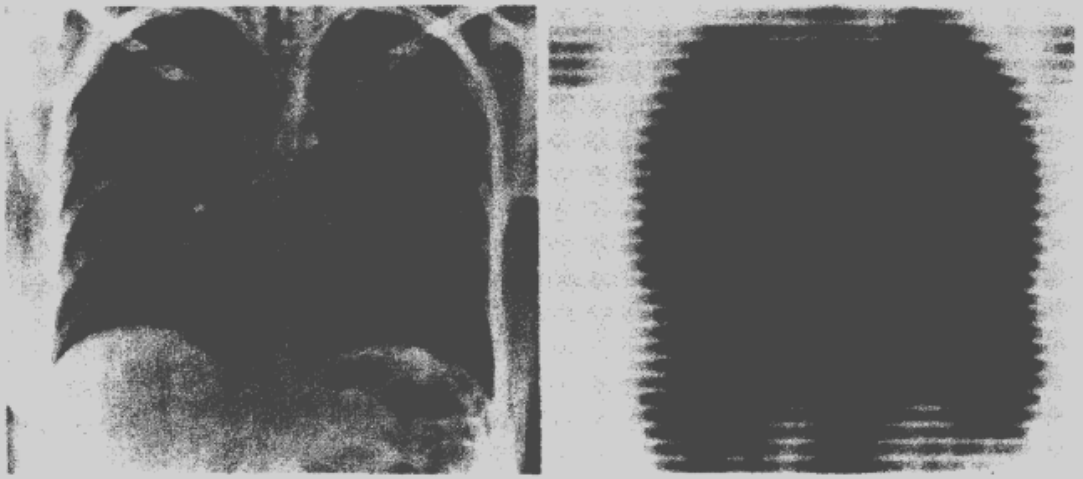
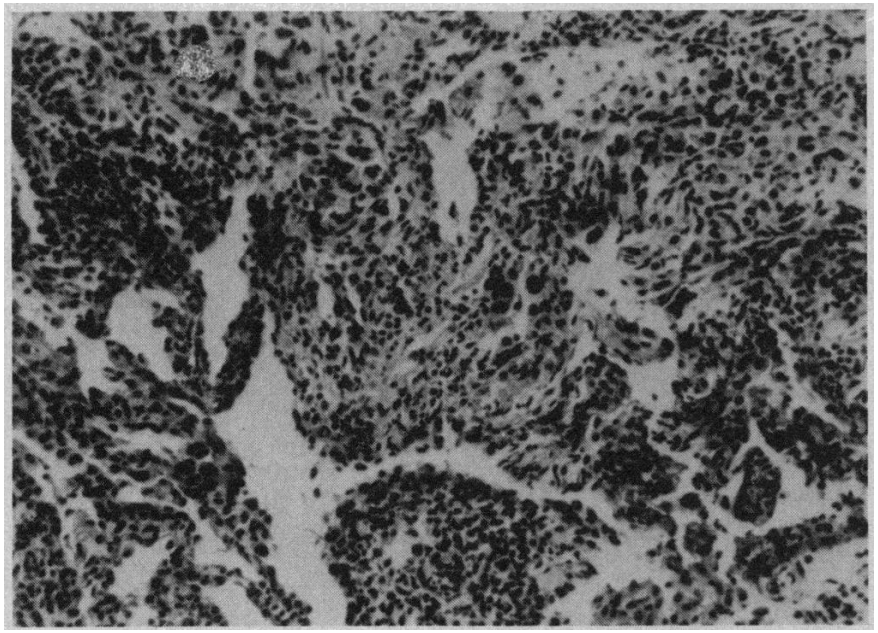
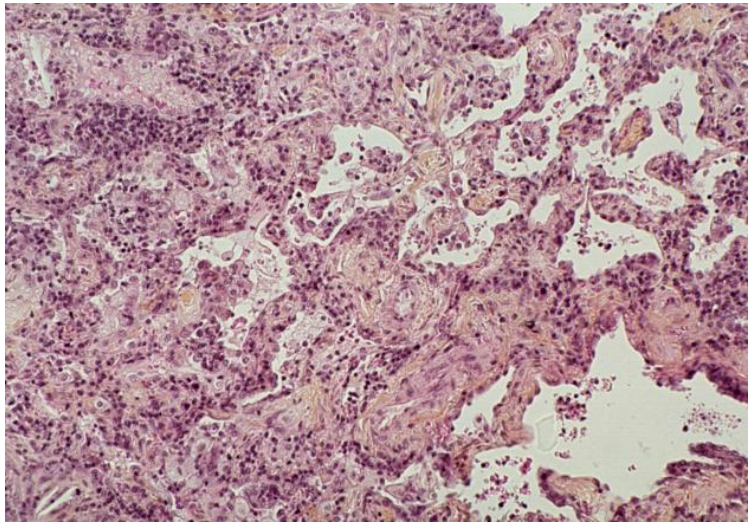


Fig 1.—Case 1. Chest roentgenogram shows minimal interstitial infiltrates (left). Gallium scan shows marked diffuse uptake in lungs (right).



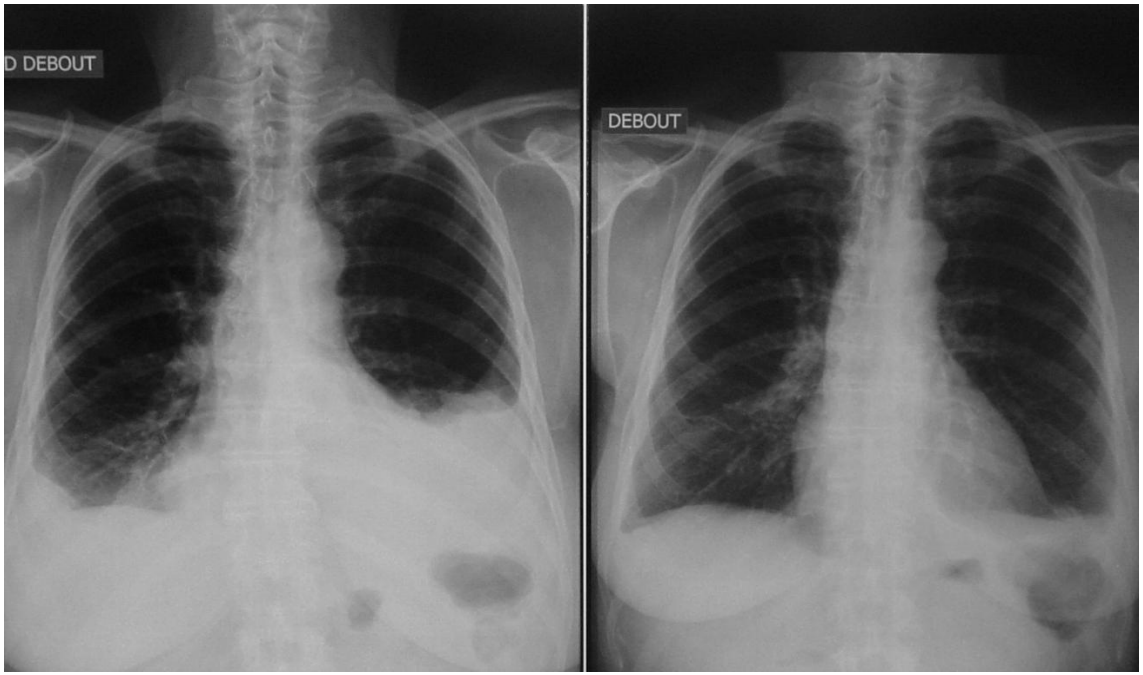
Later: minor residual changes <-> pulmonary fibrosis

- E.g. mitomycin lung



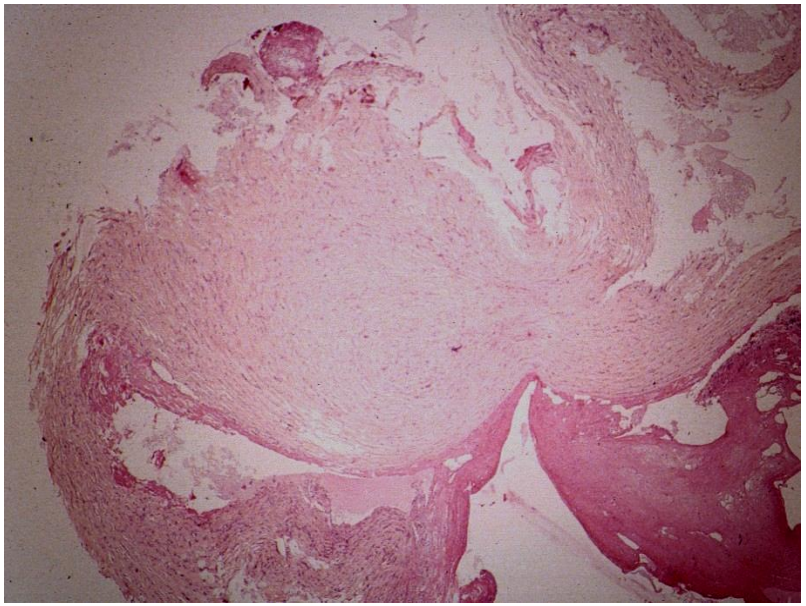
1960s DI lone, isolated pleural effusion

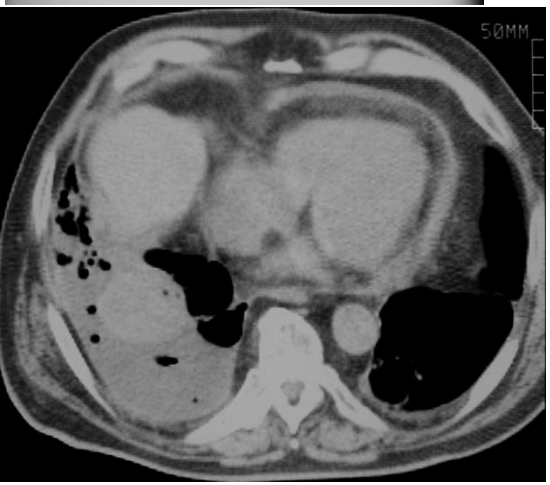
- W/wo the *lupus* syndrome (ANA)
- W/wo pericardial effusion
- Amiodarone
- Dasatinib
- Dantrolene
- Now: 91 drugs



1960s: DI pleural thickening

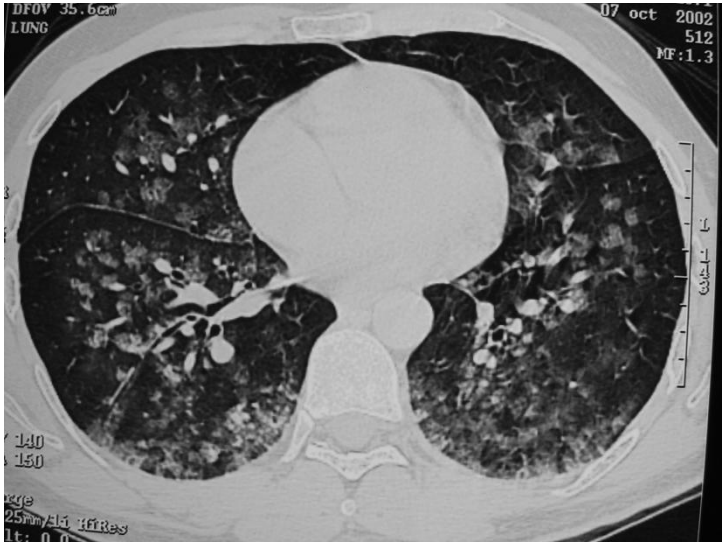
- Ergots (methysergide, bromocriptine, pergolide)

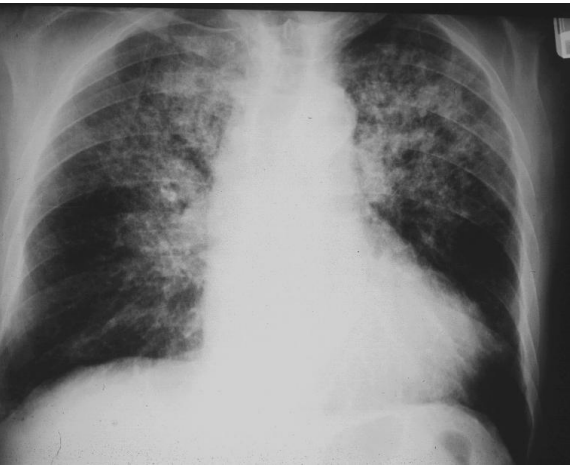


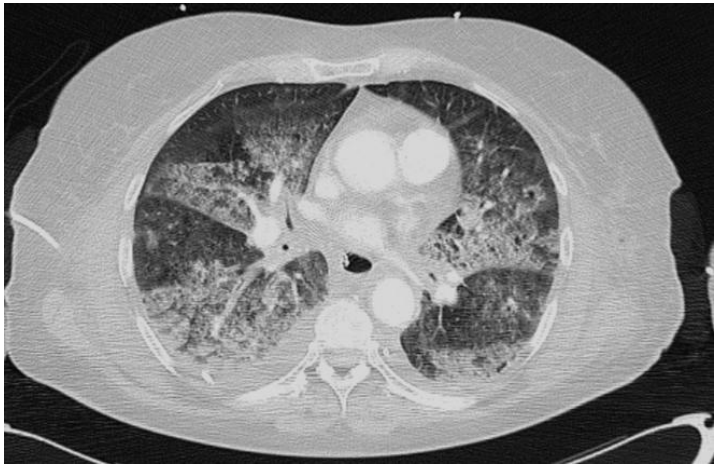


1960s: DI pulmonary edema

- Noncardiac (now 213)
  - Contrast media, aspirin
    B2 agonists, drug overdose
- Cardiogenic (now 42)
  - DI heart failure
  - Immune checkpoint inh.

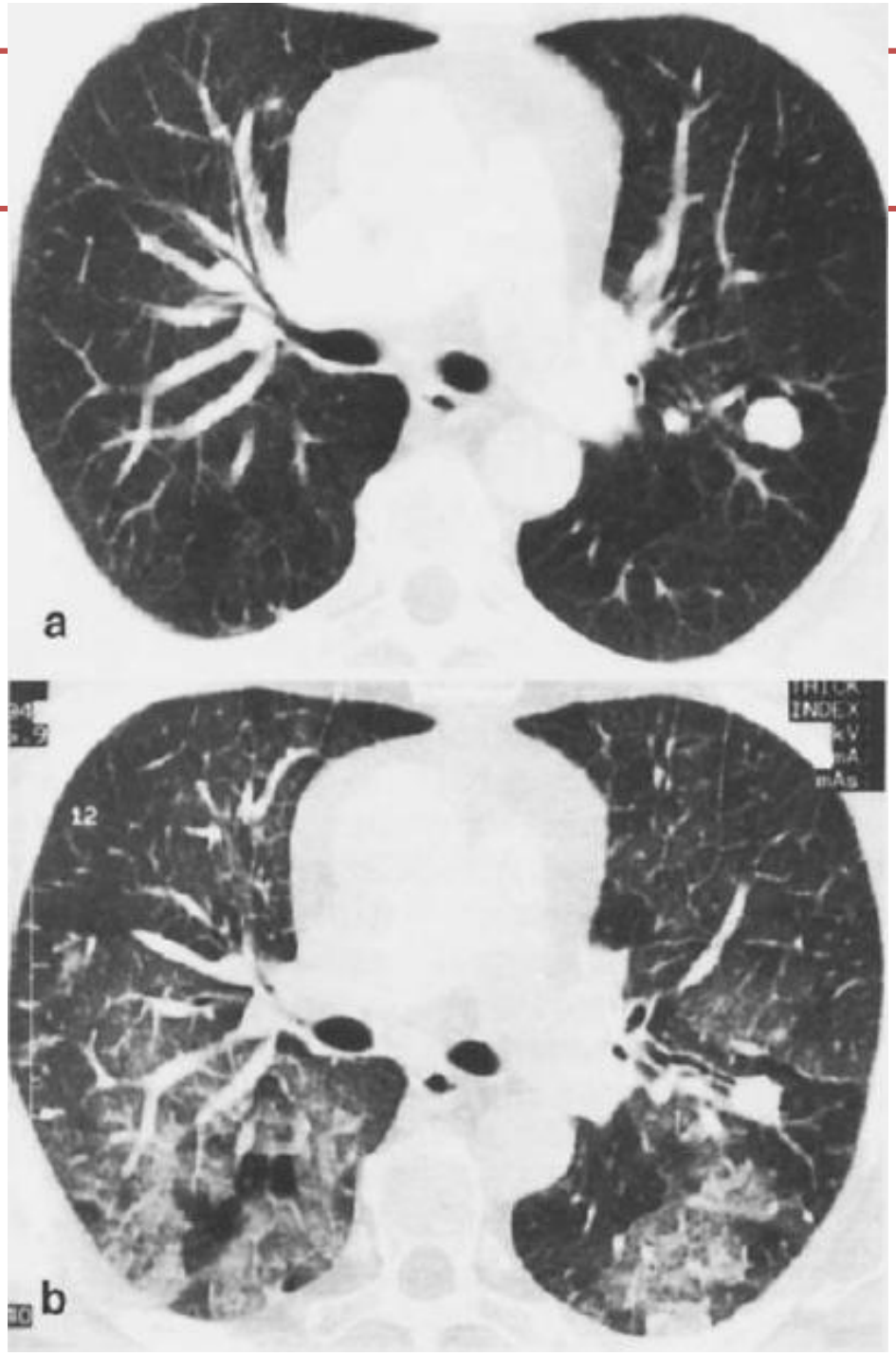






Delay can be very quick

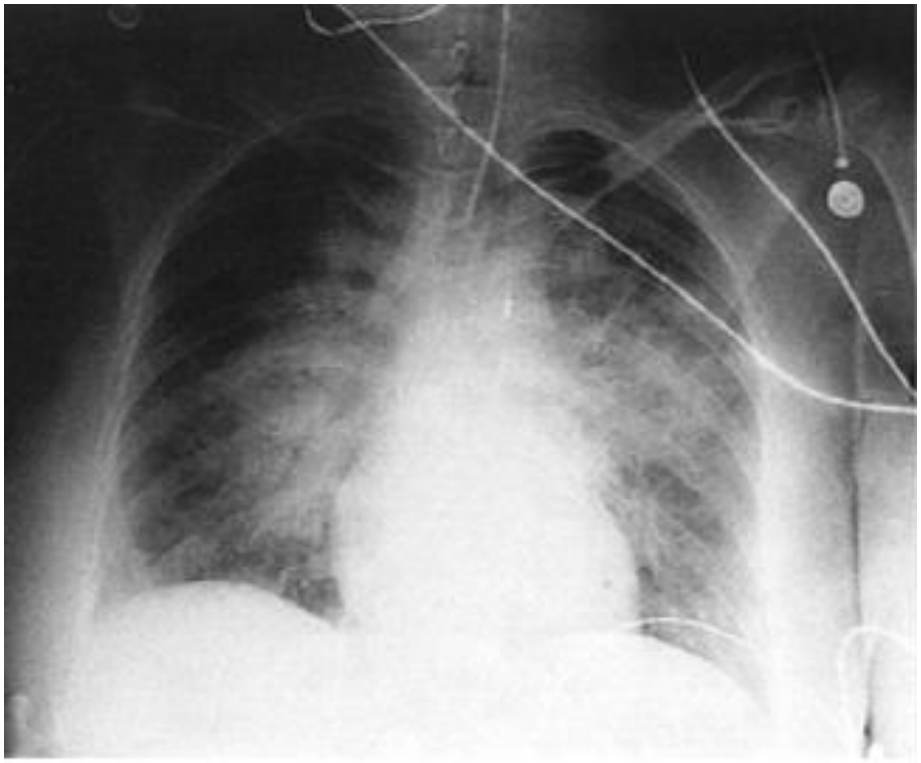
- 23s > RCM



1970s DI DAH (now 144)

- W/wo ANCA

- Vit-K antagonists
- Superwarfarins
- DOAC
- Platelet inhibitors
- Amiodarone
- Chemo agents
- Cocaine, crack, heroin
- Fluid silicone
- E-cigarette

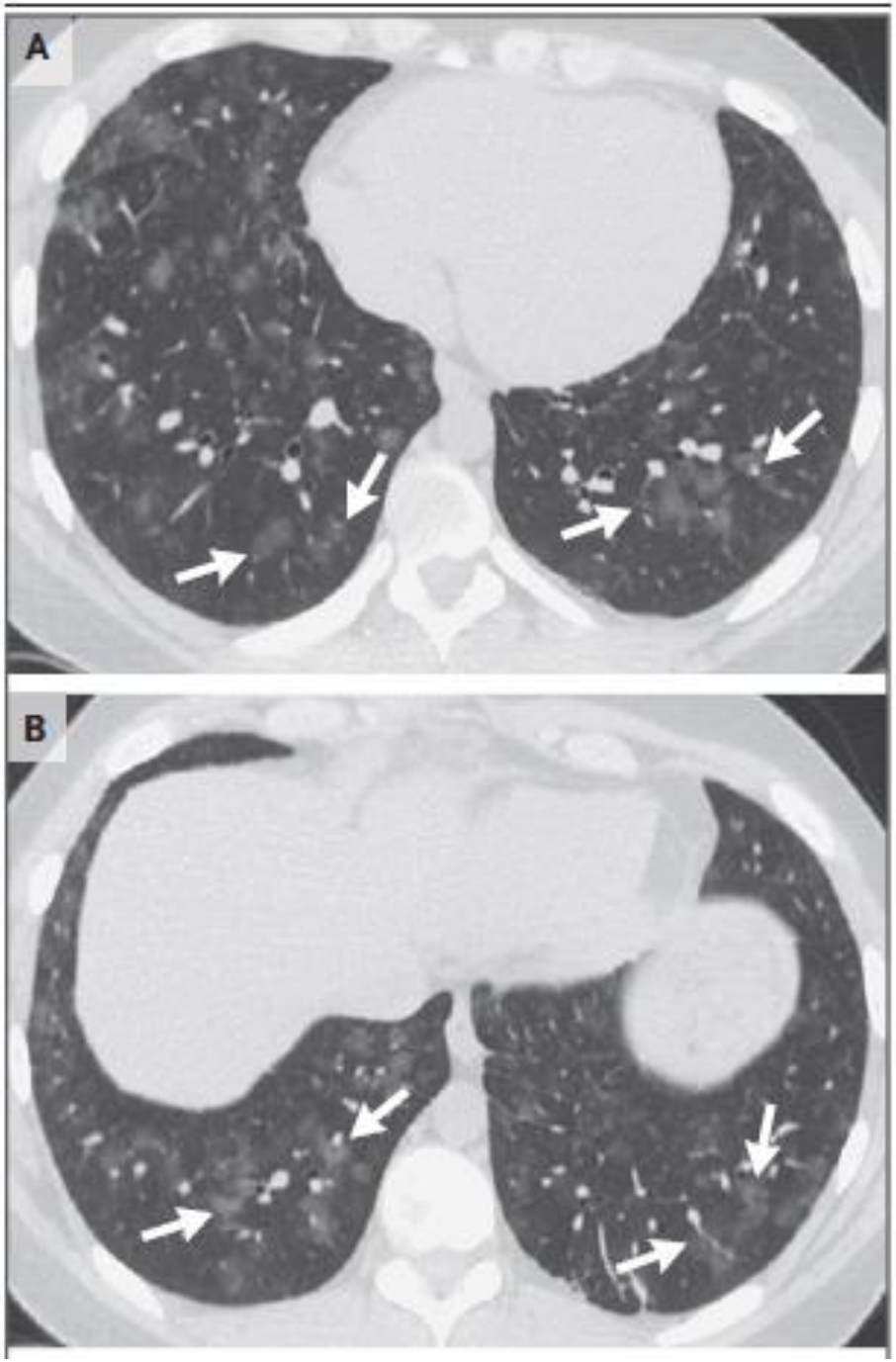


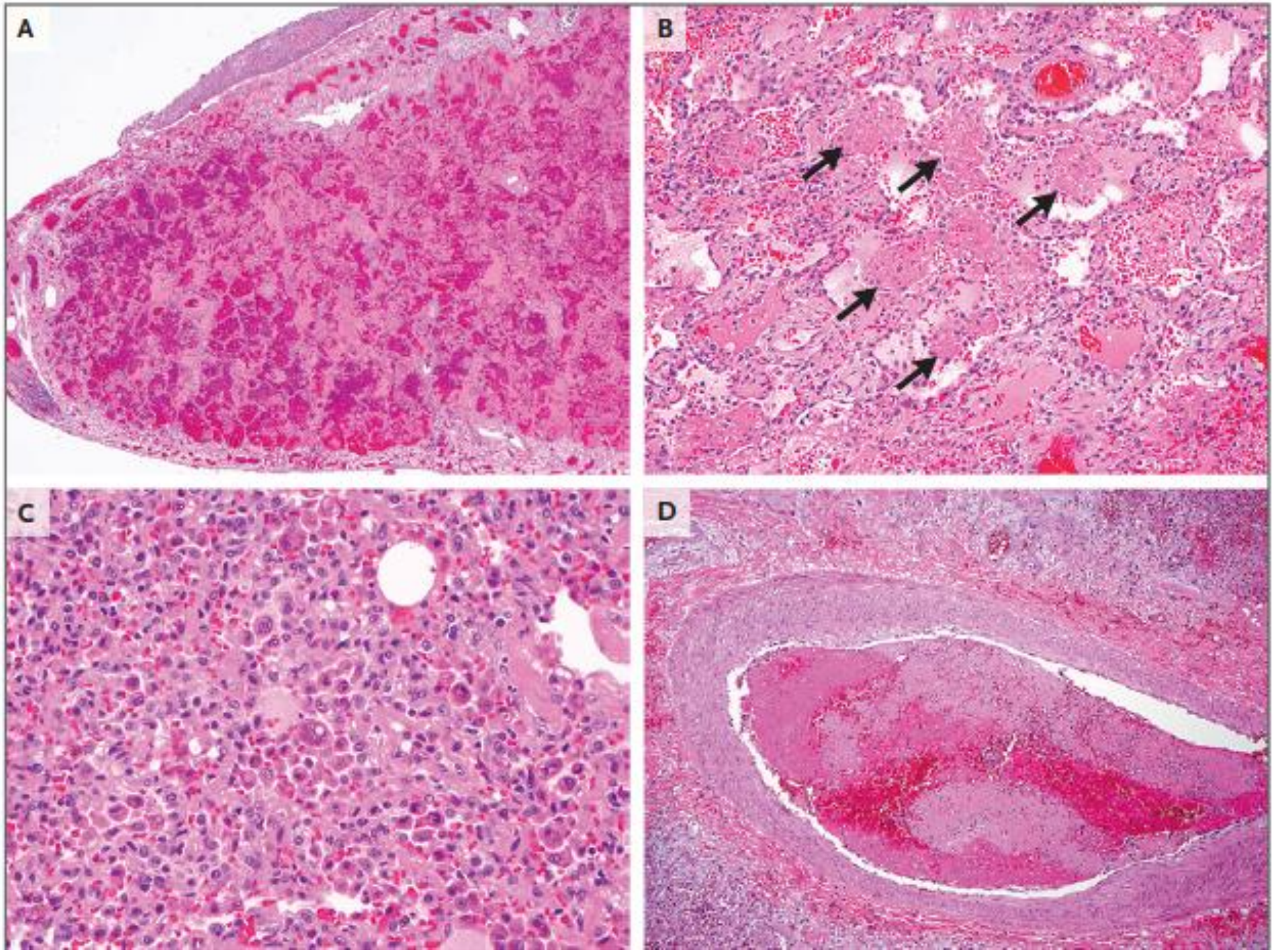
The NEW ENGLAND JOURNAL of MEDICINE

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 38-2019: A 20-Year-Old Man with Dyspnea and Abnormalities on Chest Imaging

Robert W. Hallowell, M.D., Michael B. Feldman, M.D., Ph.D.,
Brent P. Little, M.D., Rebecca S. Karp Leaf, M.D., and Lida P. Hariri, M.D., Ph.D.


A
B


A
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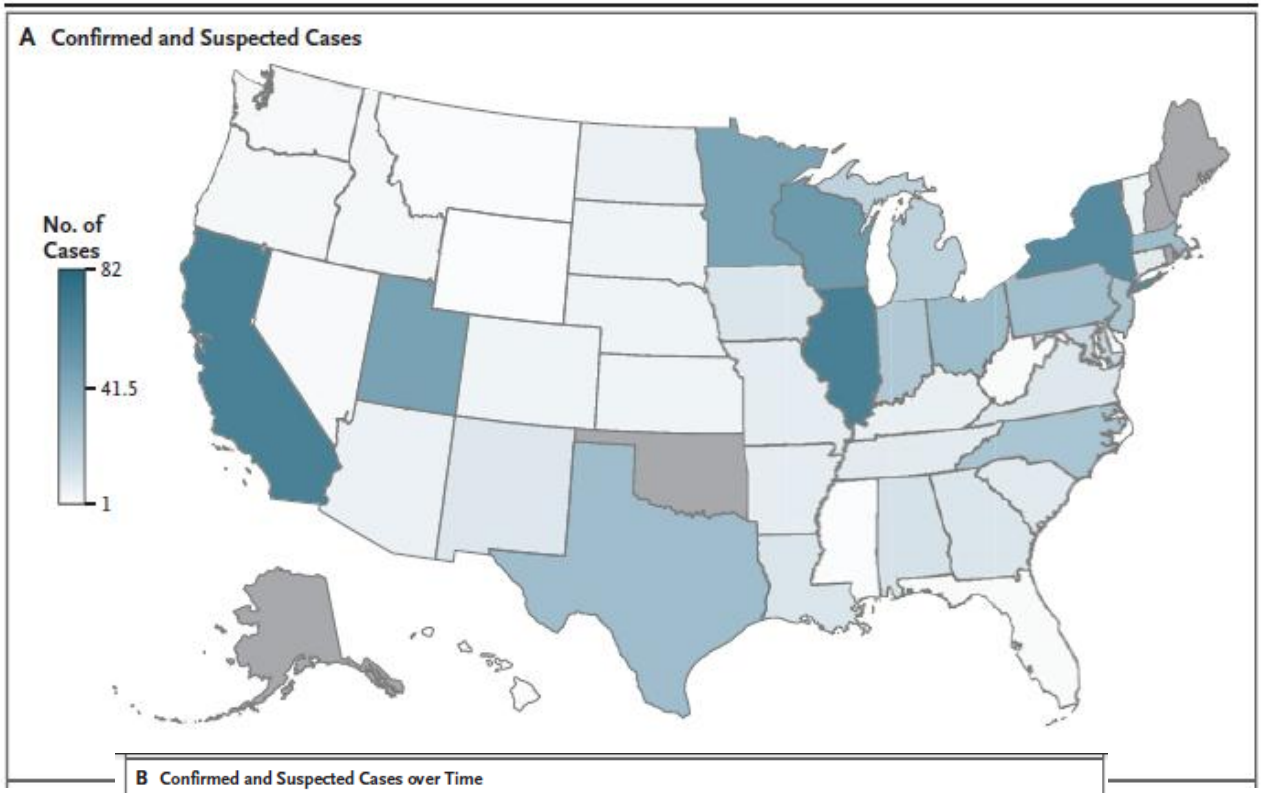
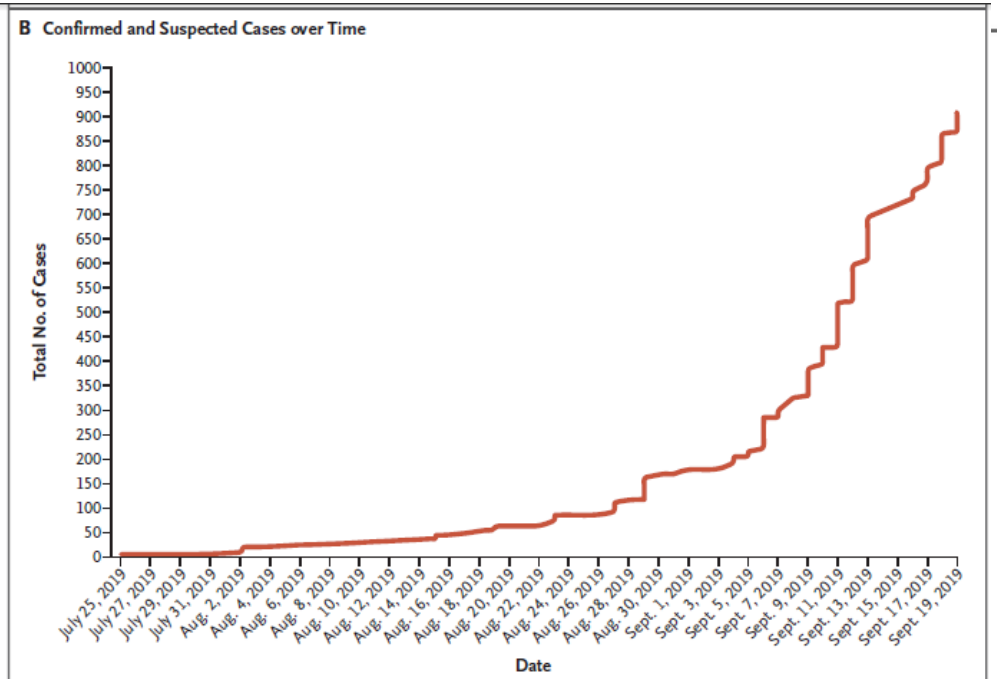
SPORTS


A Confirmed and Suspected Cases
No. of Cases
82
41.5
1


B Confirmed and Suspected Cases over Time
Total No. of Cases
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
July 25, 2019
July 27, 2019
July 29, 2019
July 31, 2019
Aug. 2, 2019
Aug. 4, 2019
Aug. 6, 2019
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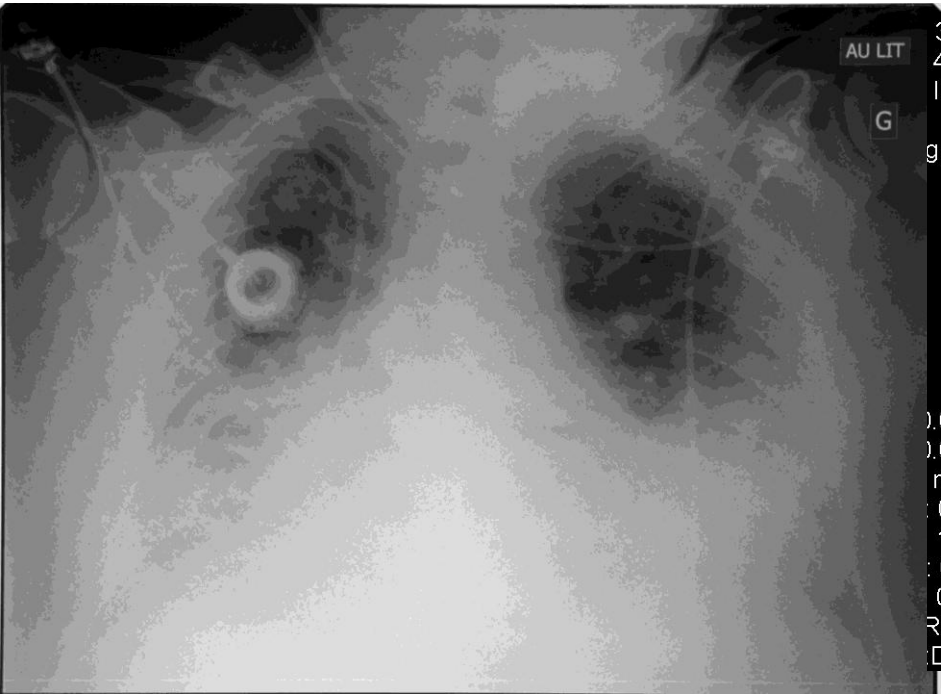
Aug. 24, 2019
Aug. 26, 2019
Aug. 28, 2019
Aug. 30, 2019
Sept. 1, 2019
Sept. 3, 2019
Sept. 5, 2019
Sept. 7, 2019
Sept. 9, 2019
Sept. 11, 2019
Sept. 13, 2019
Sept. 15, 2019
Sept. 17, 2019
Sept. 19, 2019
Date

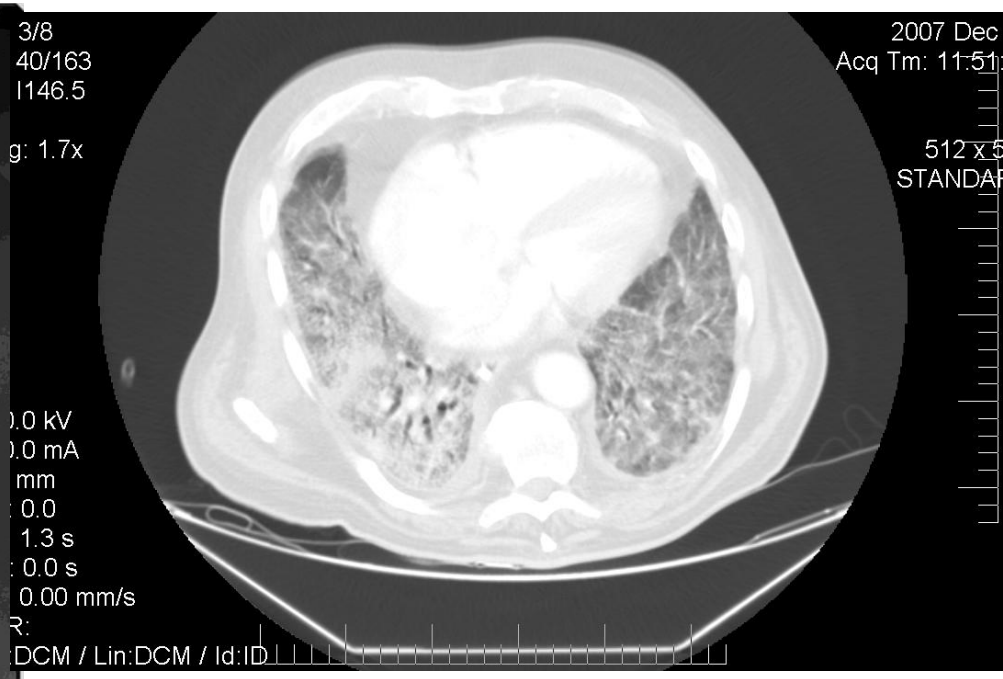
1970s

CLINICAL STUDY WITH BLEOMYCIN

SACHIDANANDA SHASTRI, MD,* ROBERT E. SLAYTON, MD† JANET WOLTER, MD,‡
CHARLES P. PERLIA, MD,§ AND SAMUEL G. TAYLOR III, MD‖

Bleomycin is an antitumor antibiotic produced by *Streptomyces verticillus*. Seventy-five patients with various neoplasms were studied using this drug. Fourteen out of 20 patients with epidermoid carcinoma of the head and neck region, 5 out of 14 cases of lymphoma including Hodgkin's disease, 3 out of 6 patients with testicular tumors, and one patient with lymphangiosarcoma of the arm showed evidence of objective regression. Common side effects encountered were hyperthermic reactions, gastrointestinal disturbances, hyperkeratosis and vesiculation of fingers, alopecia, and stomatitis. Pulmonary fibrosis is a rare but serious complication. One patient in this series died of this complication. There was no evidence of bone marrow, liver, or renal toxicity. Bleomycin promises to be a useful therapeutic agent and merits further study.





Aminorex-induced PHTn

BRITISH MEDICAL JOURNAL 30 JANUARY 1971

Drug-induced Pulmonary Hypertension?

F. FOLLATH, F. BURKART, W. SCHWEIZER

British Medical Journal, 1971, 1, 265–266

Summary

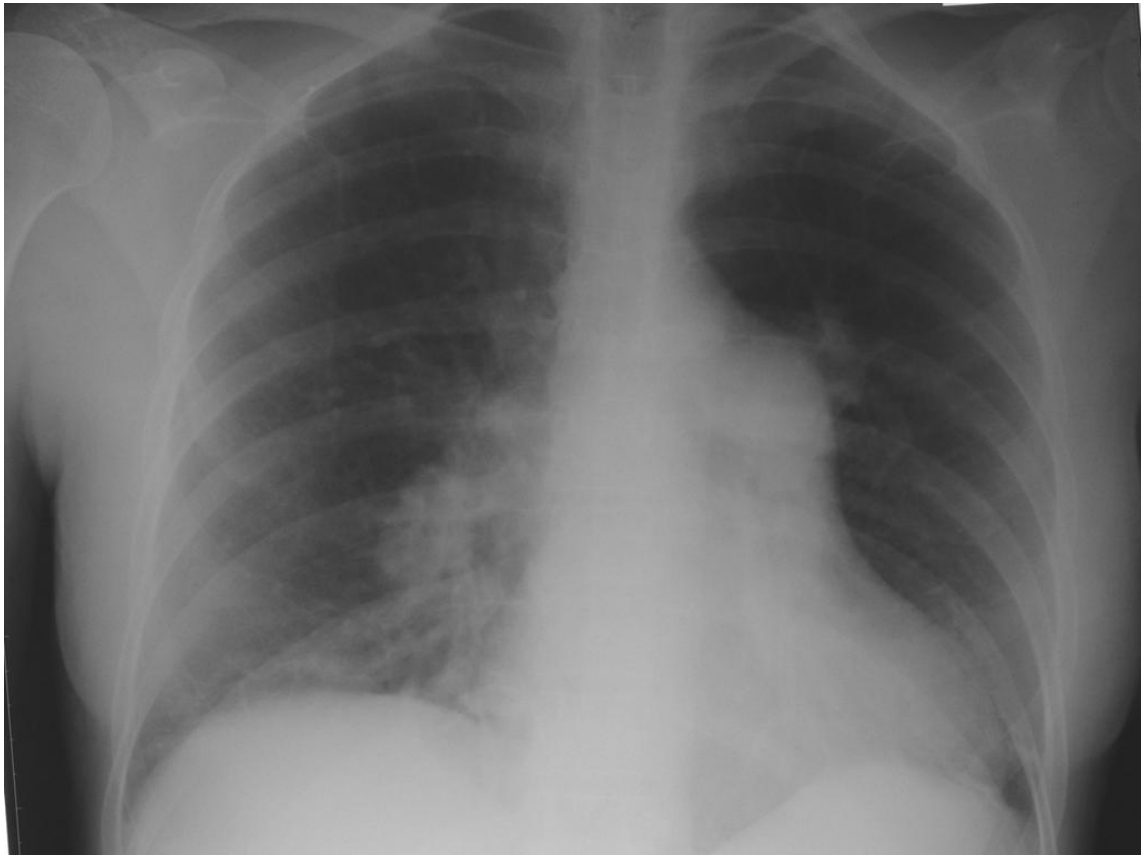
Of 40 patients with obstructive pulmonary hypertension studied in Basle, Switzerland, during the period 1966-68, 32 had been taking an anorectic drug, aminorex fumarate. Rapidly progressing exertional dyspnoea, central chest pain, and syncope on effort were characteristic features. The absence of the usual causes of pulmonary vascular disease seems to suggest the possibility of drug-induced pulmonary hypertension. Further studies are necessary, however, to clarify the role of aminorex fumarate in this condition.

had recognized pulmonary
postpartum, one during a
unknown cause). All others
present illness. A feature
prolonged intake of the an
- amino - 5 - phenyl - 2
been widely used in Switz
(Table I). The treatment
one year in 11, 6-12 month
patients. In most the dysp
the intake of aminorex fu
used oral contraceptives.

A large "a" wave in th

Precapillary PHTn (now 70)

- Aminorex
- Fenfluramine
- Dexfenfluramine
- Benfluorex
- Amphetamines
- Dasatinib
- Ponatinib
- Bosutinib



Methotrexate lung

- Mostly acute
  - Hemato-oncology
  - Rhumatology ~1%/patient/year
  - BAL: Ly & exclusionary for *Pneumocystis*
- Withdrawal and corticosteroids
- Can relapse with rechallenge (fatalities)

Magnitude of the Problem

- 1973: John L Stauffer: 120 drugs/769 papers

Medical Staff Conference

Refer to: Drug-induced lung disease: The price of progress—Medical Staff Conference, University of California, San Francisco. Calif Med 119:48-55, Oct 1973

Drug-Induced Lung Disease:

The Price of Progress

J Stauffer Chief-Resident 1973

TABLE 2.—*Patterns of Drug-Induced Lung Disease*

1. Pulmonary fibrosis
2. Pulmonary edema
3. Asthma
4. Hypersensitivity reactions
5. Respiratory failure
6. Opportunistic infections
7. Pulmonary embolism
8. Pulmonary infiltrates
9. Mediastinal and hilar disease
10. Fever
11. Aspiration pneumonia
12. Systemic lupus erythematosus
13. Nitrofurantoin lung disease
14. Oxygen toxicity
15. Miscellaneous

TABLE 3.—*Drugs That May Cause Pulmonary Fibrosis*

Busulfan (Myleran®)
Cyclophosphamide (Cytoxan®)
Hexamethonium
Mecamylamine (Inversine®)
Pentolinium (Ansolysen®)
Methysergide (Sansert®)
Bleomycin
?Diphenylhydantoin (Dilantin®)
Nitrofurantoin (Furadantin®)

TABLE 4.—*Drugs That May Cause Pulmonary Edema*

Heroin (smack)
Methadone (Dolophine®)
Propoxyphene (Darvon®)
Hydrochlorothiazide (Hydrodiuril®)
Epinephrine (Adrenalin®)
Phenylbutazone (Butazolidin®)

TABLE 5.—*Drugs That May Cause Asthma*

Penicillin	Nitrofurantoin (Furadantin®)
Tetracycline	Reserpine
Erythromycin	Antisera
Neomycin	Vaccines
Streptomycin	Allergenic extracts
Griseofulvin	Aspirin
Cephaloridine (Keflin®, Loridine®)	Histamine phosphate
Ethionamide (Trecator®)	Methacholine (Mecholyl®)
Monoamine oxidase inhibitors (Parnate®)	Acetylcysteine (Mucomyst®)
Radio-opaque organic iodides	Calcium gluconate
Local anesthetics	Disodium cromoglycate (Cromolyn®)
Mercurials	Polymyxin B
Vitamin K	Isoproterenol (Isuprel®)
Bromsulphalein	Propranolol (Inderal®)
Sodium dehydrocholate (Decholin®)	Pituitary snuff
Iron dextran (Imferon®)	?Synthetic lysine vasopressin
Prostaglandin F_2A	Hashish
Pentazocine (Talwin®)	Succinylcholine
Indomethacin (Indocin®)	d-Tubocurarine
	Gallamine (Flaxedil®)

TABLE 6.—*Drugs That May Cause Respiratory Failure*

Central Nervous System Depression	*Respiratory Muscle Paralysis*
Sedatives and hypnotics	Neomycin
Oxygen in patients with hypercapnia	Streptomycin
Heroin	Kanamycin
Alcohol	Gentamicin
THAM	Polymyxin B
Antihistamines	Colistin
Anesthetics	Succinylcholine
	Curare, quinine, and quaternary ammonium compounds

TABLE 7.—*Drugs Associated with Pulmonary Infiltrates*

With Eosinophilia	*Without Eosinophilia*
Aminosalicylic acid (PAS)	Methotrexate (Amethopterin®)
Isoniazid (INH)	Azathioprine (Imuran®)
Penicillin	Paraquat
Nitrofurantoin (Furadantin®)	Illicit drugs
Aurothioglucose (Solganal®)	Procarbazine (Matulane®)
Mephenesin carbonate (Tolseram®)	
Poison ivy allergen	
Chlorpropamide (Diabinese®)	
Disodium cromoglycate (Cromolyn®)	
Aspirin	
Sulfonamides	
Imipramine (Tofranil®)	
Pituitary snuff	

TABLE 8.—*Drugs That May Cause Systemic Lupus Erythematosus*

Procaine amide (Pronestyl®)	Gold salts
Hydralazine (Apresoline®)	Diphenylhydantoin (Dilantin®)
Isoniazid (INH)	Mephenytoin (Mesantoin®)
Penicillin	Propylthiouracil
Tetracycline	Methylthiouracil
Sulfonamides	Thiazides
Streptomycin	Reserpine
Griseofulvin	Methyldopa (Aldomet®)
Aminosalicylic acid (PAS)	Oral contraceptives
Phenylbutazone (Butazolidin®)	Digitalis

TABLE 9.—*Drugs Associated with Miscellaneous Reactions in the Lungs*

Polyarteritis:
- Iodides
- Arsenicals
- Mercurials
- Hydantoins
- Penicillin
- Guanethidine (Ismelin®)
- Gold salts
- Thiouracils
- Phenothiazines
- Sulfonamides
- Hydralazine (Apresoline®)

Pulmonary calcification:
- Calcium gluconate
- Vitamin D

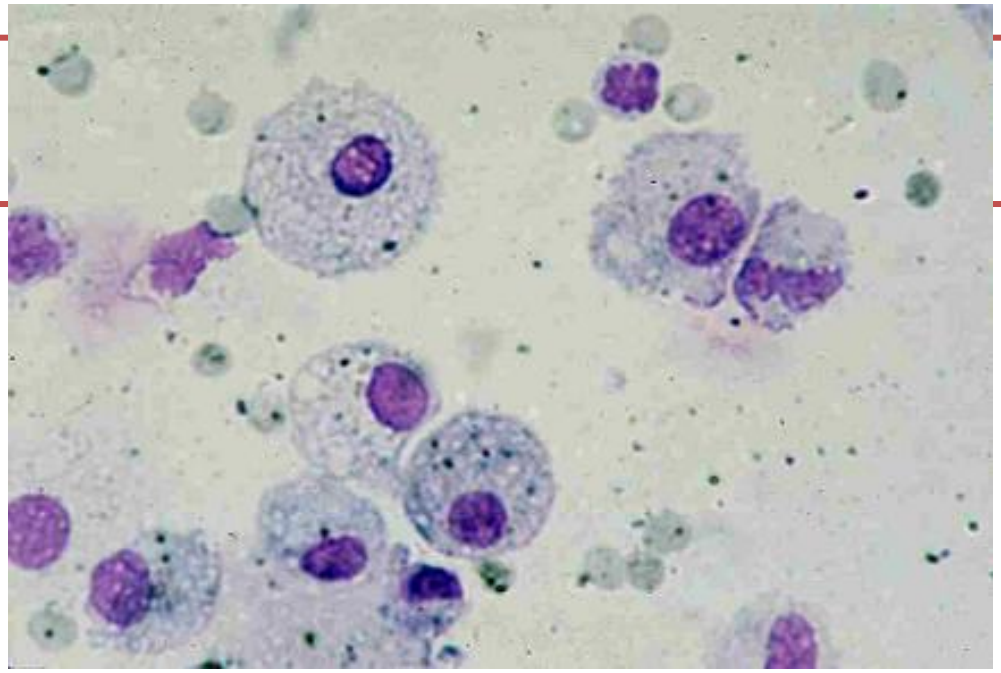
Necrotizing vasculitis:
- Illicit drugs,
- ?corticosteroids

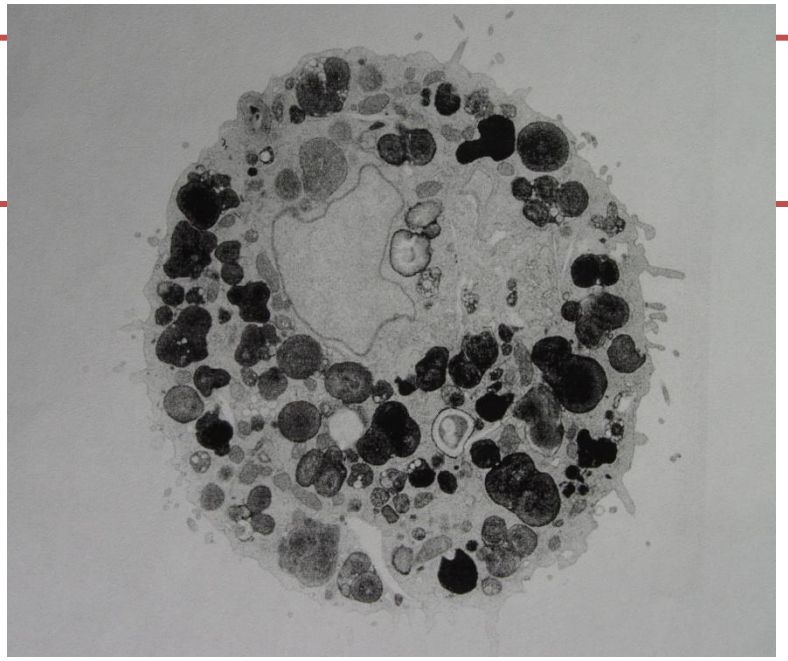
Pulmonary hypertension:
- Aminorex fumarate

Intrapulmonary hemorrhage:
- Anticoagulants

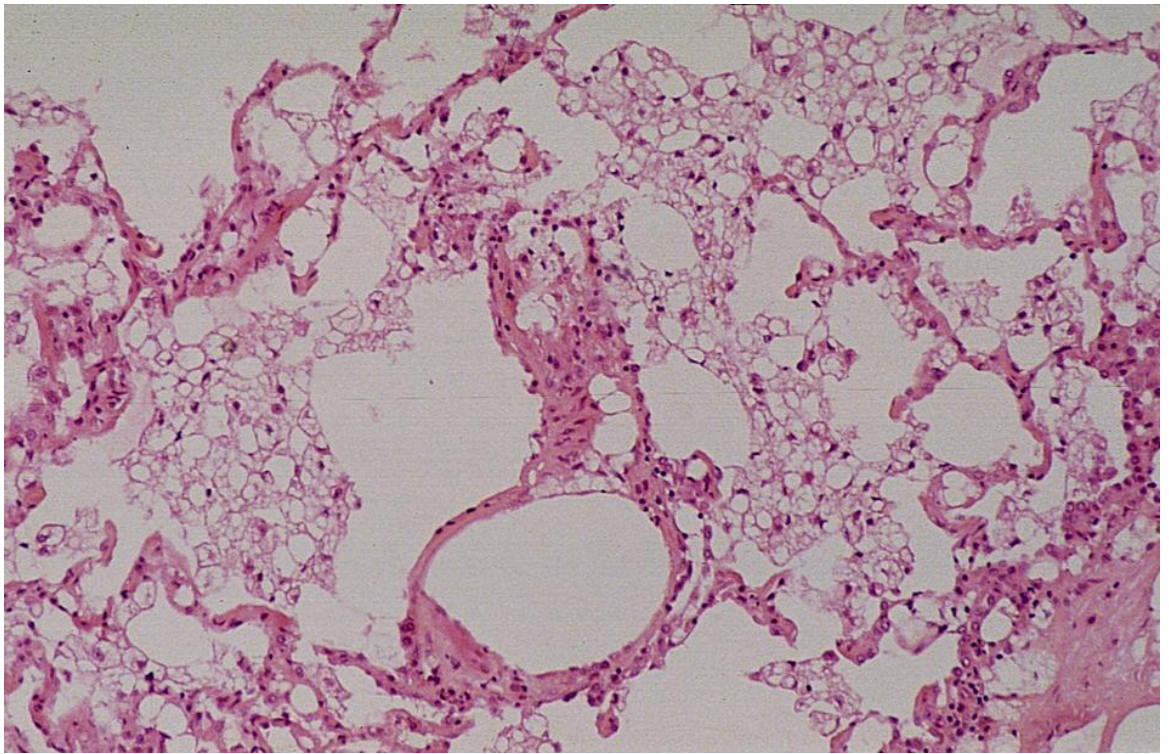
1980s: Amiodarone

- Now: 1015 papers ~2000 cases
- ~Dose-related (Ernawati *et al*. 2008: n=237)
- Typically male >60yo-6-12 mo-100-150g of Am
- [2 days – 14 years]
- Need be separated from LVF (imaging, echo, BNP, diuresis) - Both may coexist
- BAL: ‘some contribution’
- Corticosteroids often required
- Dosage – duration (60mg taper over 6-12 mo)
- Pulmonary fibrosis may follow
- Overall mortality: 10-50%

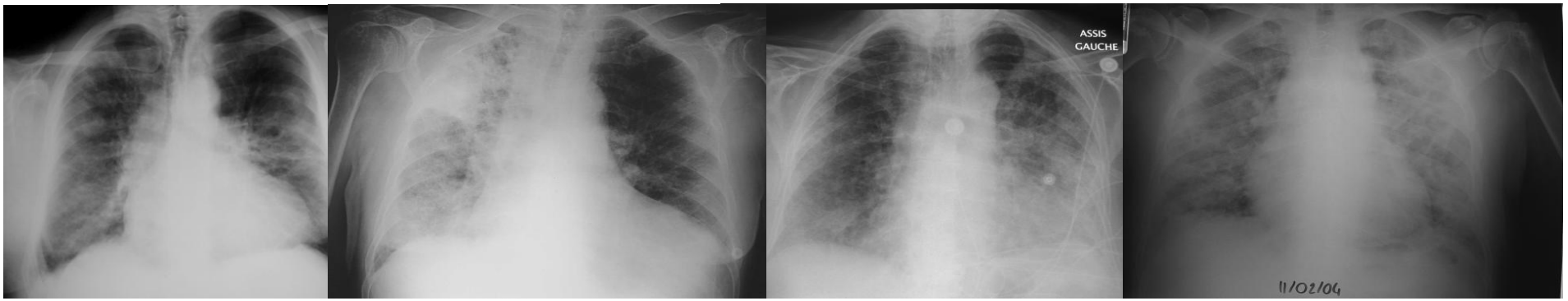


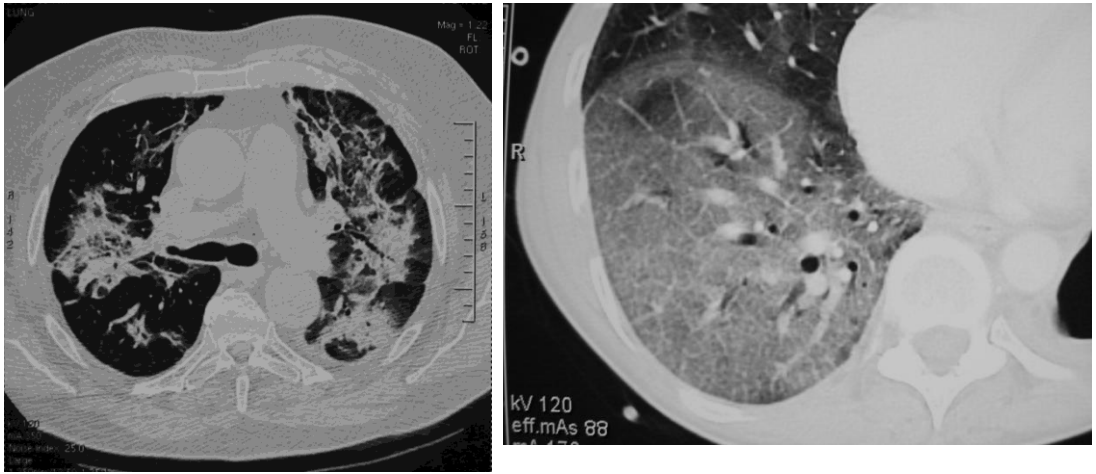


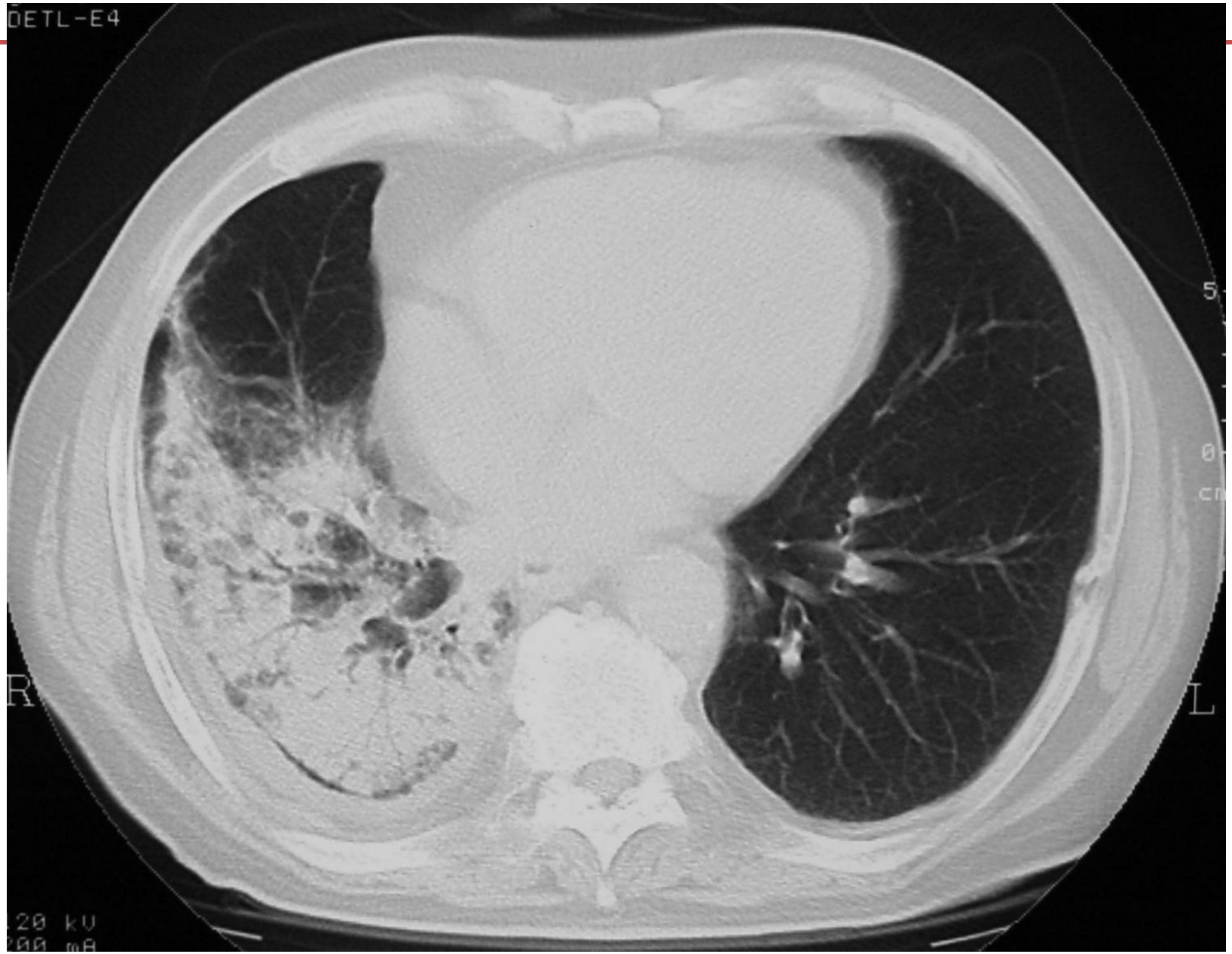
- Subclinical effect
- KCO altered



Overt AIPT: Imaging






DETL-E4
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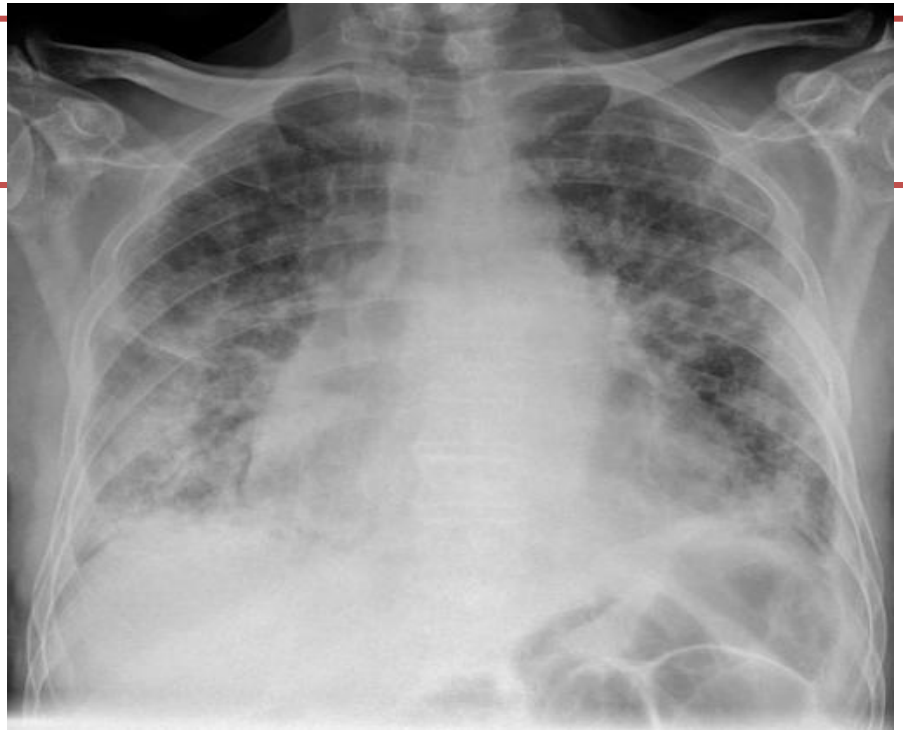
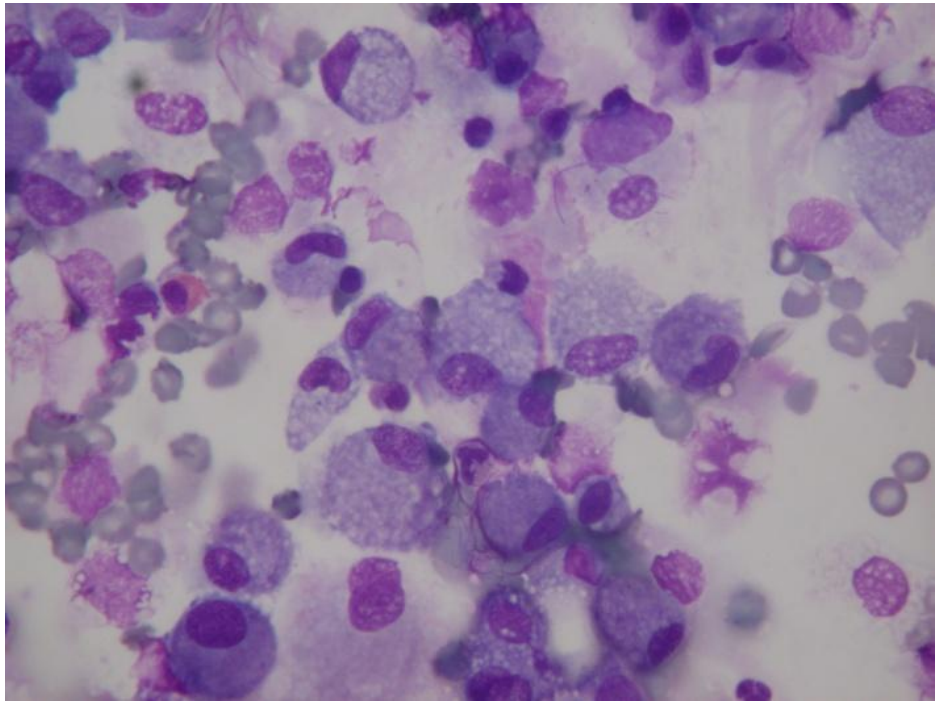
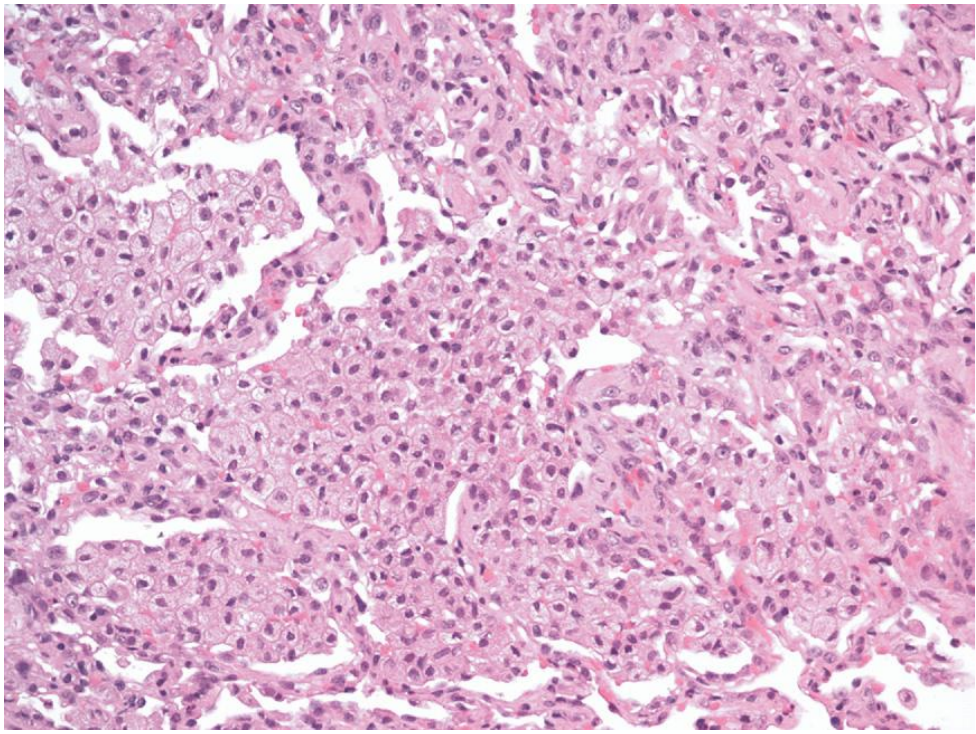


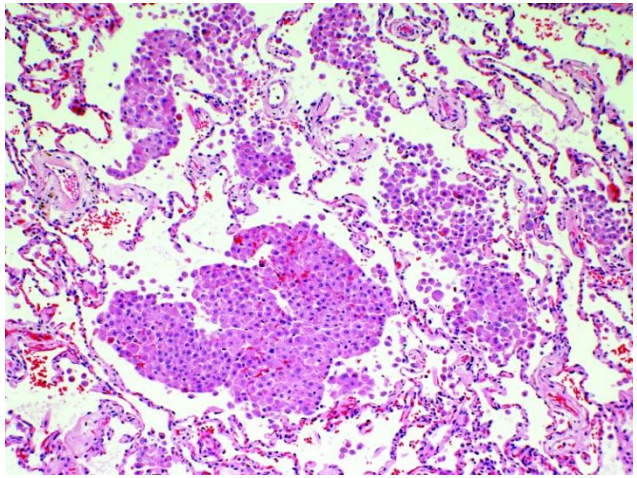

512 x 512
STANDARD
R
L
120.0 kV
154.0 mA
1.3 mm
Tilt: 0.0
ET: 0.7 s
GP: 0.0 s
TS: 0.00 mm/s

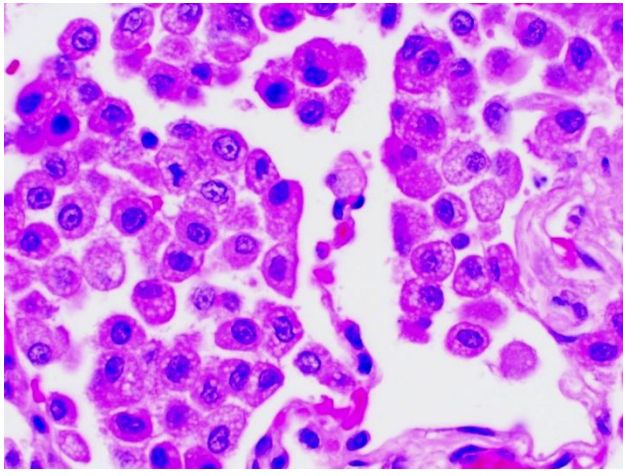
- Sir Godfrey Hounsfield
- 1919-2004

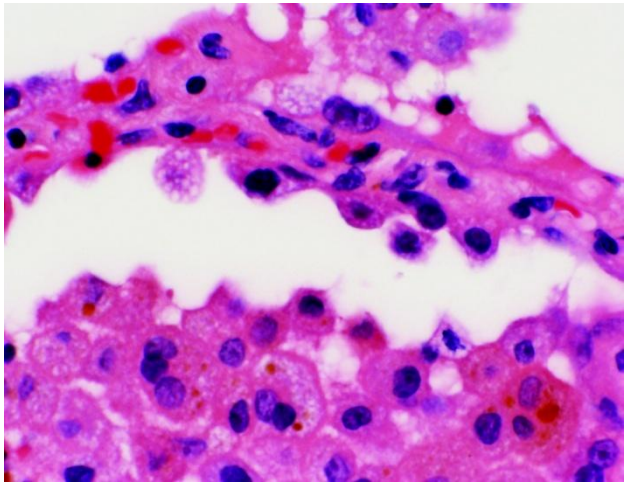

2
ARD
x
A
s
s
0 mm/s
L:30
P
DFOV: 35.9



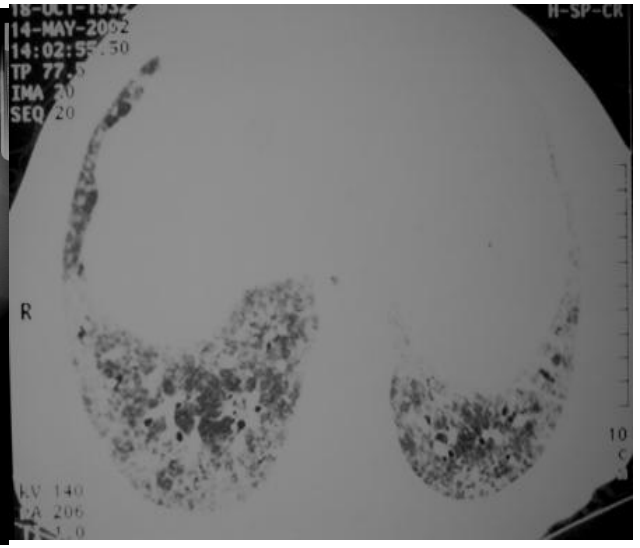


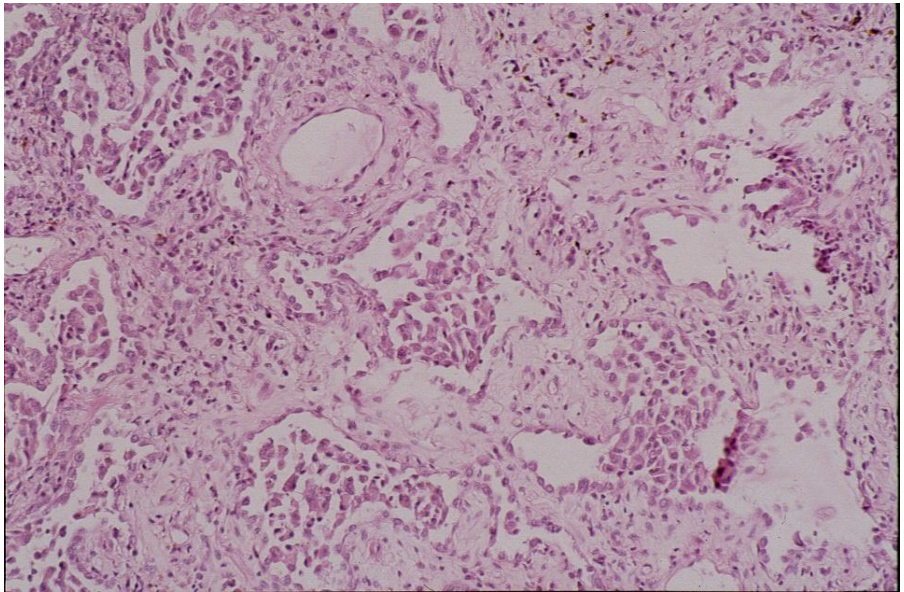


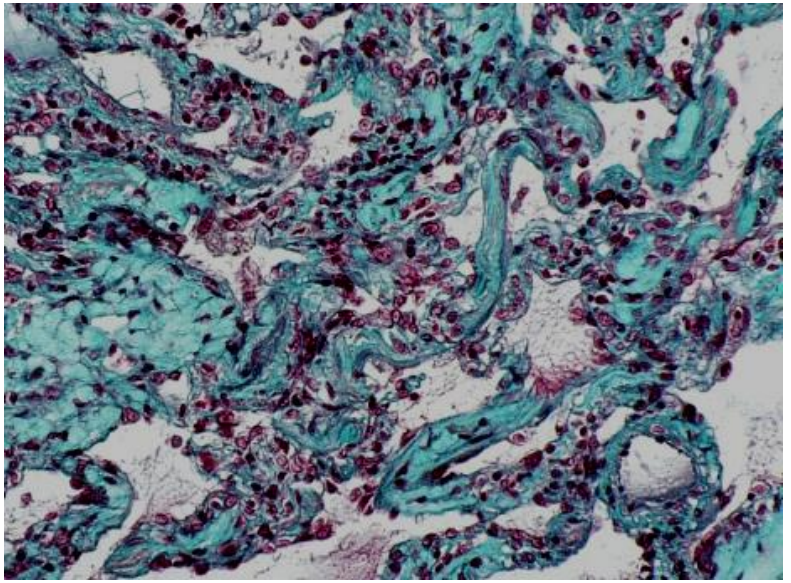




Amiodarone-associated pulmonary fibrosis





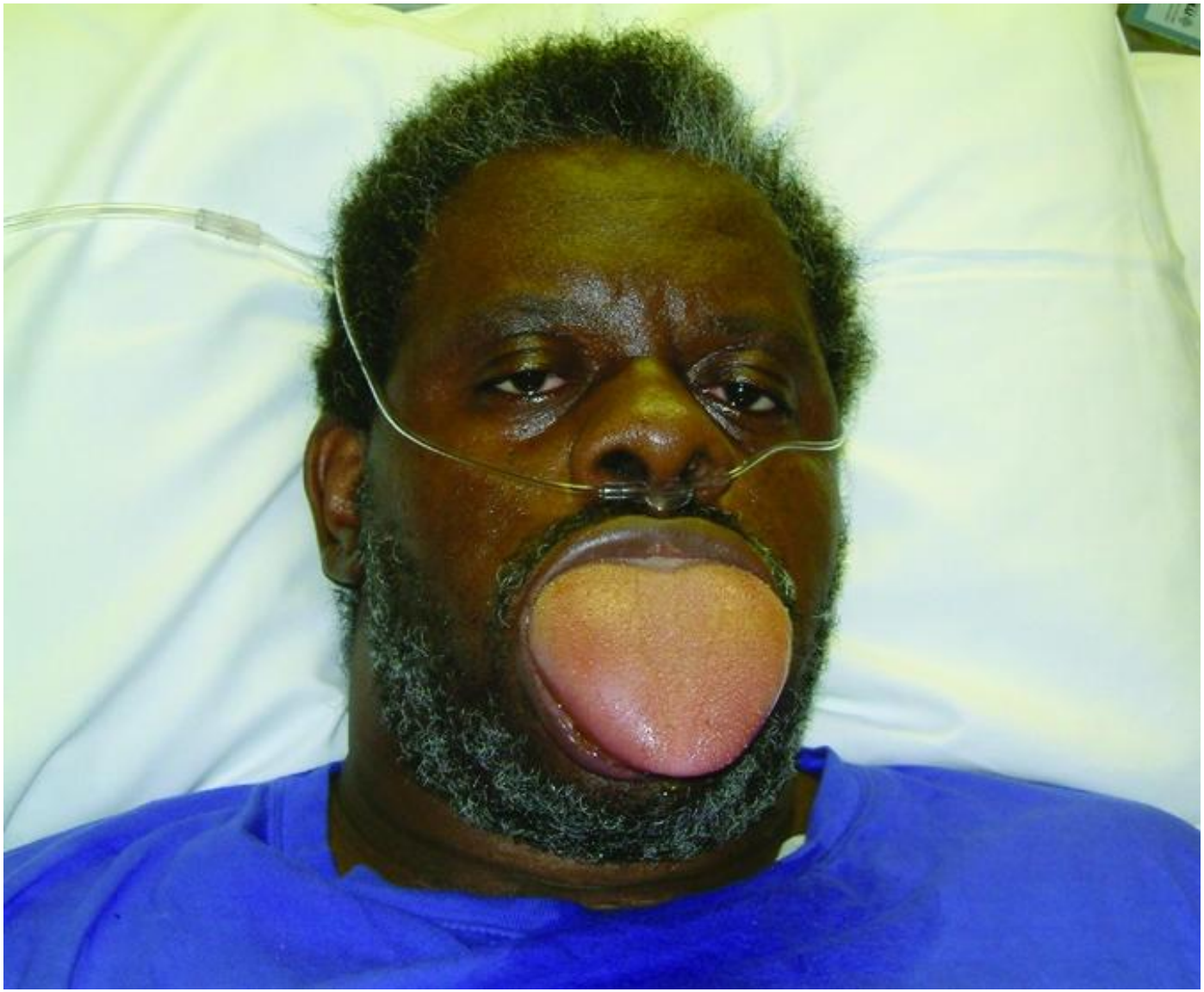


1980s

- Drug-induced cough
  - ACEI
  - Now 62

ACEI & angioedema

Angioedema – Tongue edema



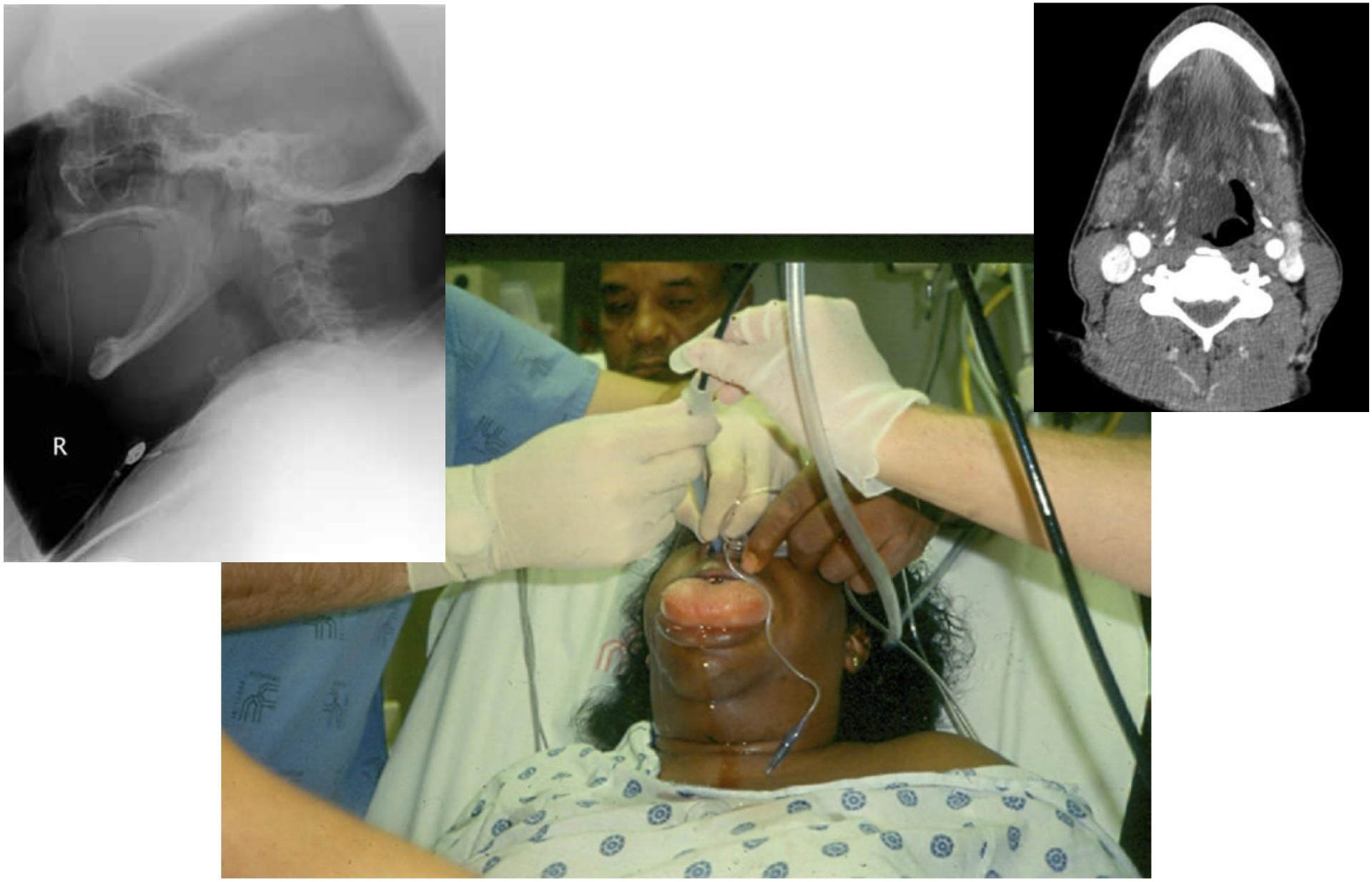
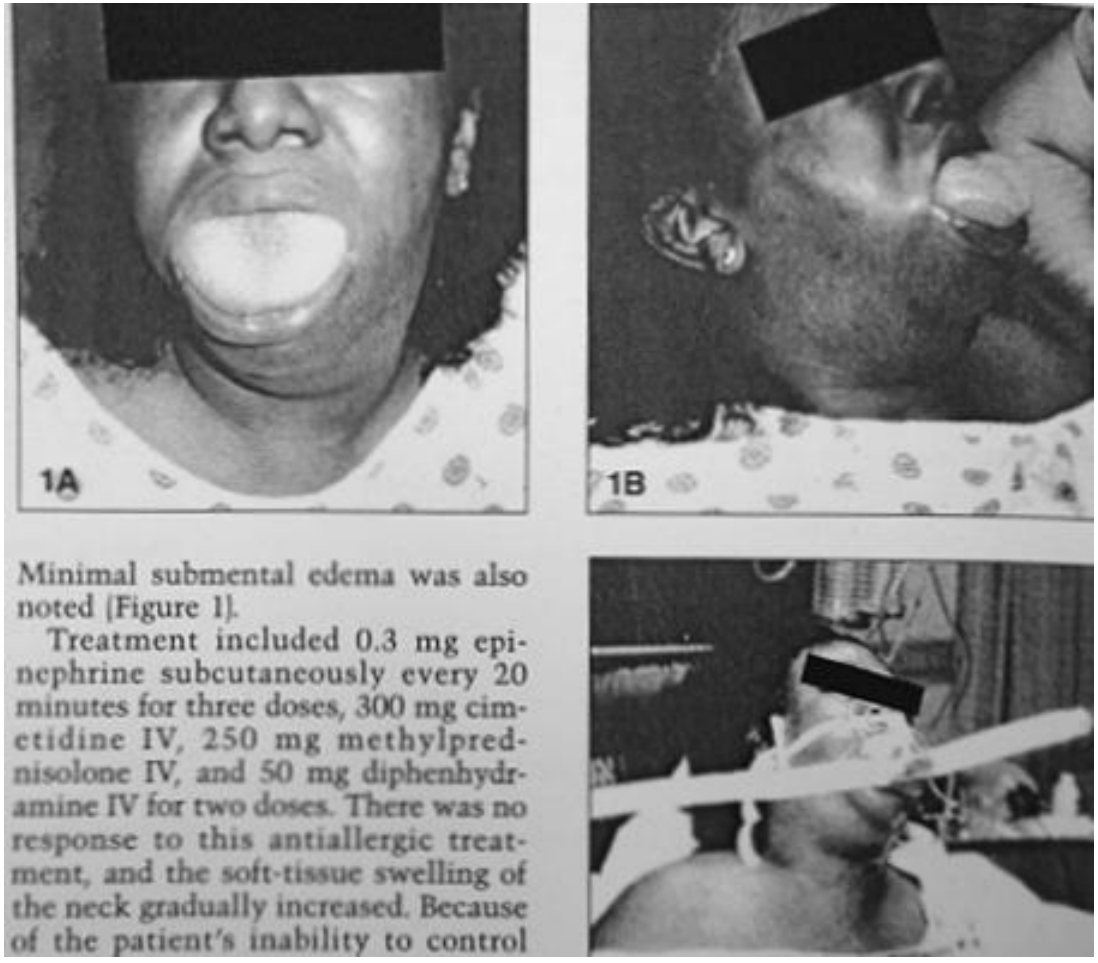


Figure 1. Example of life-threatening ACE inhibitor–induced angioedema with attempted emergency fiber optic nasotrachael intubation. The procedure was unsuccessful, and an emergency cricothyroidotomy was performed with great difficulty.

CASE REPORT

Dorothy E. Dean,[1] M.D.; Daniel L. Schultz,[2] M.D.; and Robert H. Powers,[2] Ph.D.

Asphyxia Due to Angiotensin Converting Enzyme (ACE) Inhibitor Mediated Angioedema of the Tongue During the Treatment of Hypertensive Heart Disease



Minimal submental edema was also noted (Figure 1).

Treatment included 0.3 mg epinephrine subcutaneously every 20 minutes for three doses, 300 mg cimetidine IV, 250 mg methylprednisolone IV, and 50 mg diphenhydramine IV for two doses. There was no response to this antiallergic treatment, and the soft-tissue swelling of the neck gradually increased. Because of the patient's inability to control

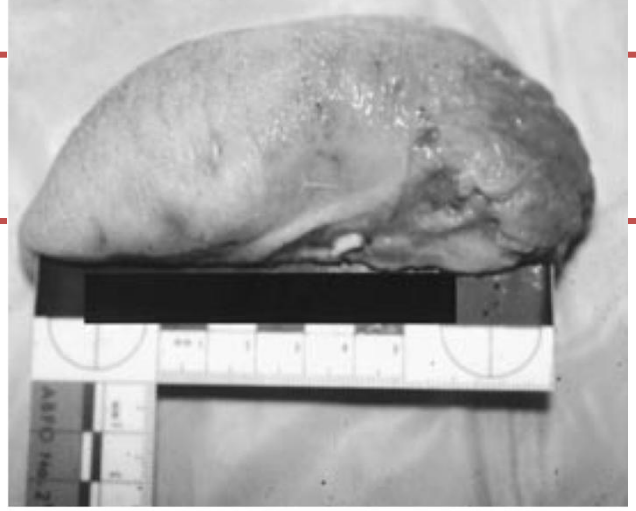
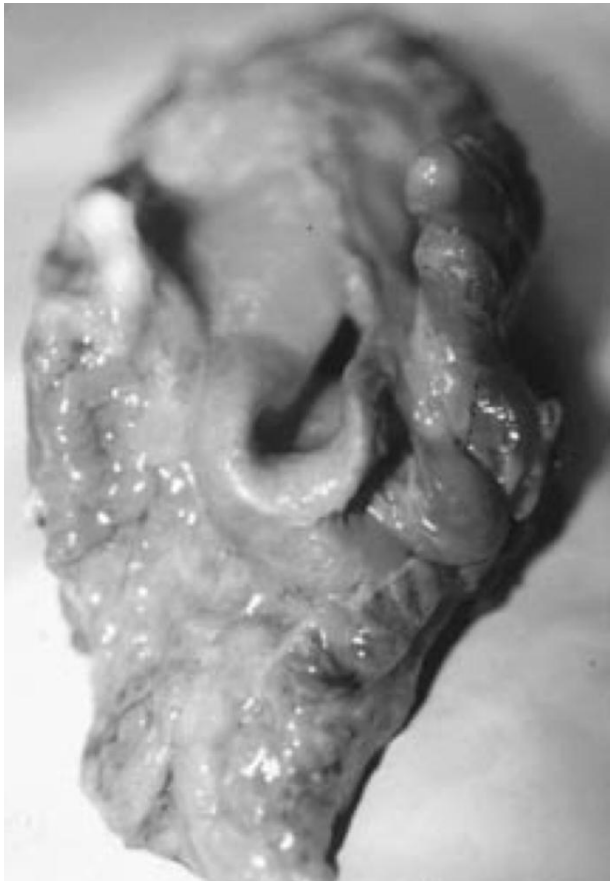


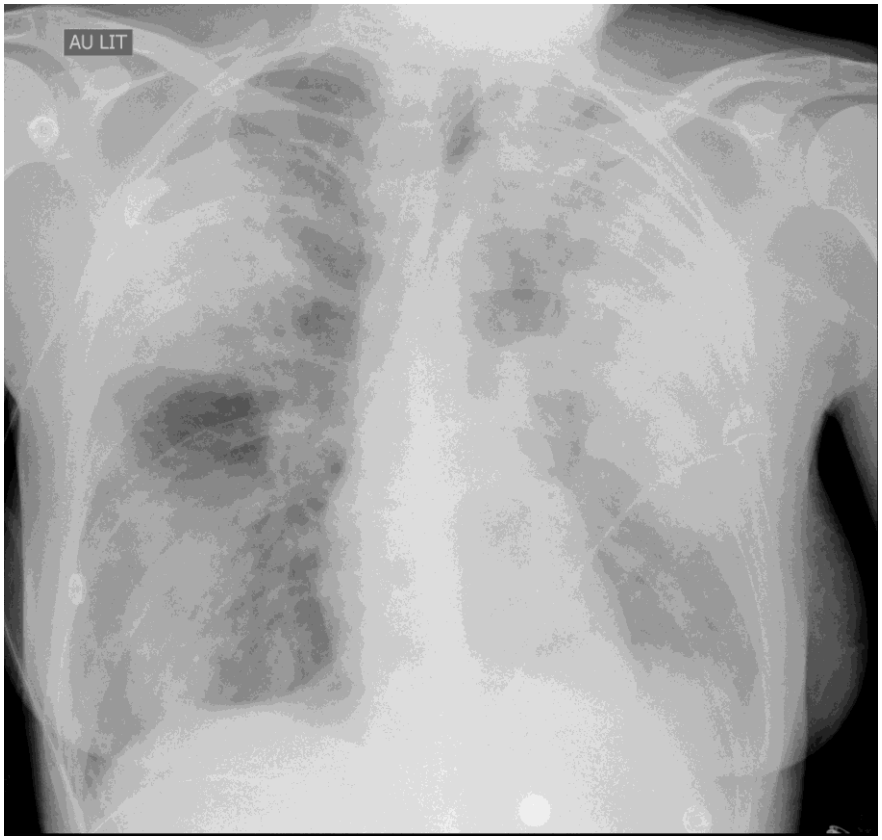
FIG. 2—*Angioedema of tongue.*

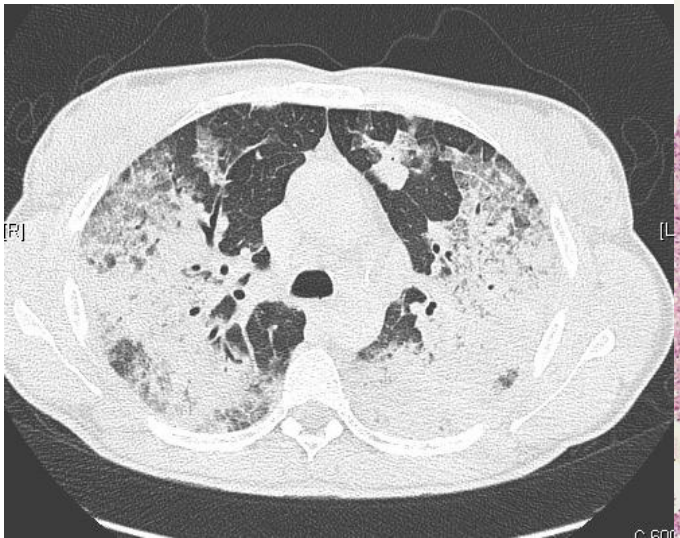


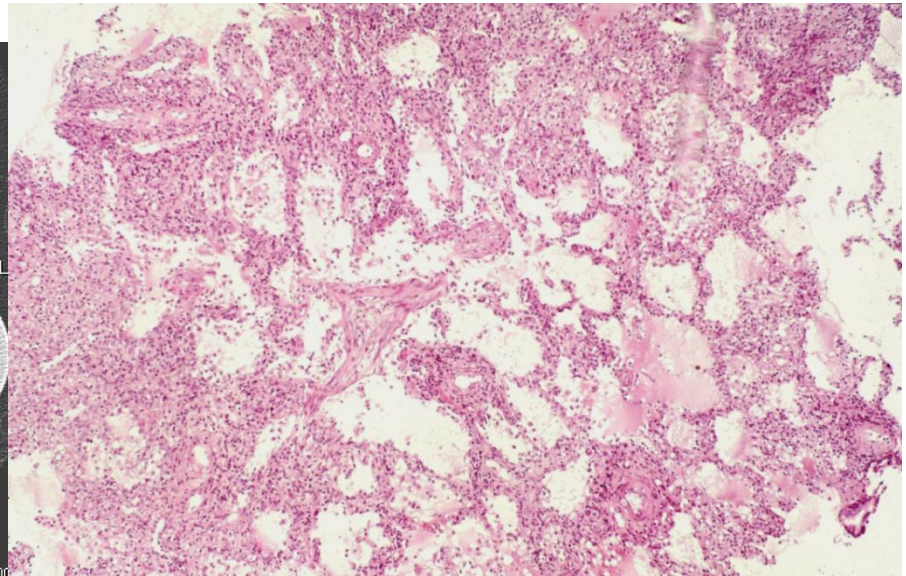
1990s

- More DI:
  - Anaphylaxis (cetuximab, oxaliplatin)
  - Eosinophilic pneumonias
  - Organizing pneumonia (BOOP) (statins, irradiation to the breast)
  - Methemoglobinemia

- AEP: now 53
  - minocycline
  - daptomycin
  - antidepressants
  - NSAIDs
  - smoking
  - marijuana
  - cocaine
  - e-cigarette

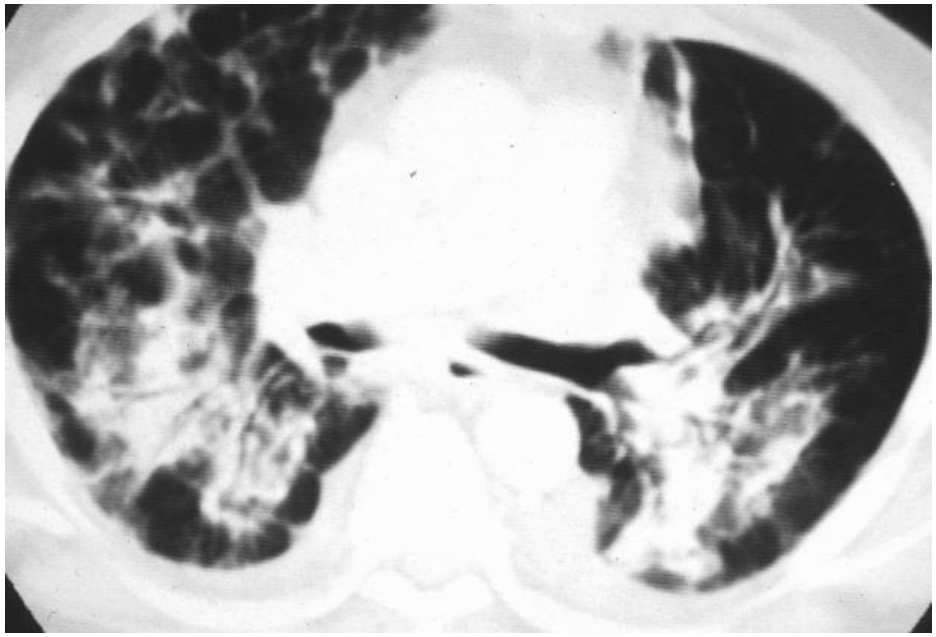


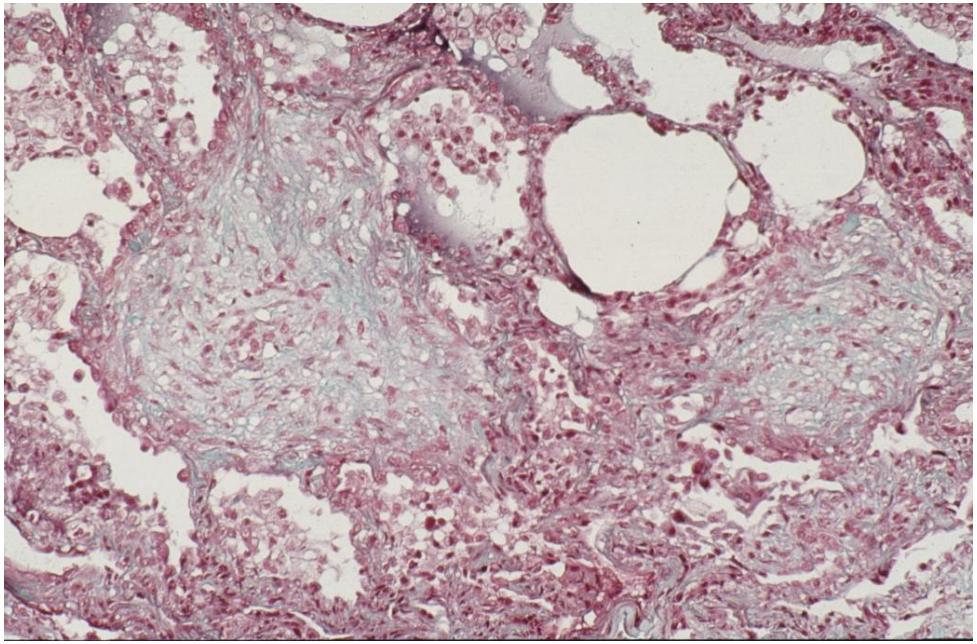


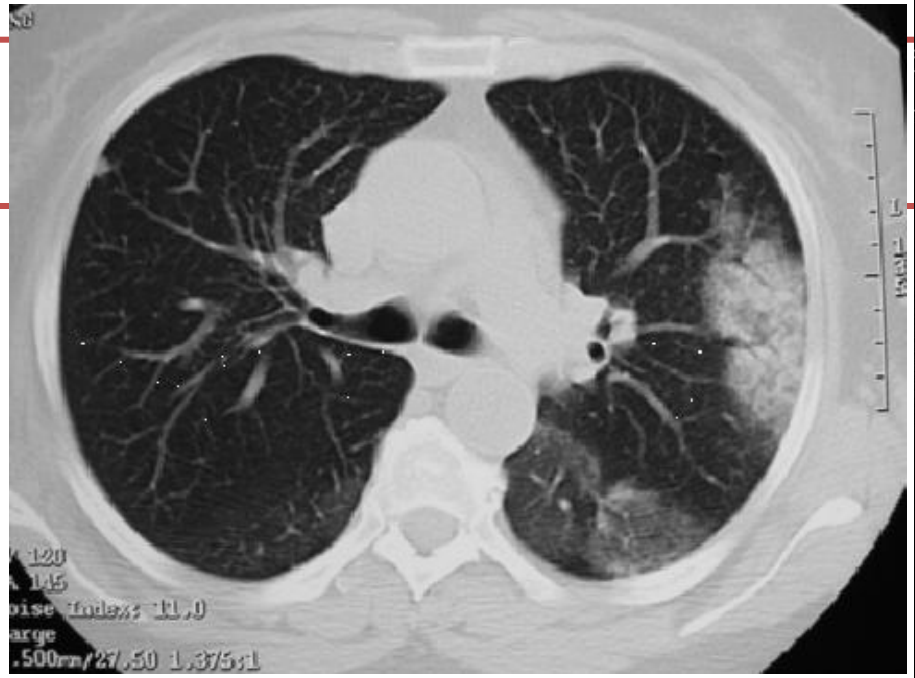


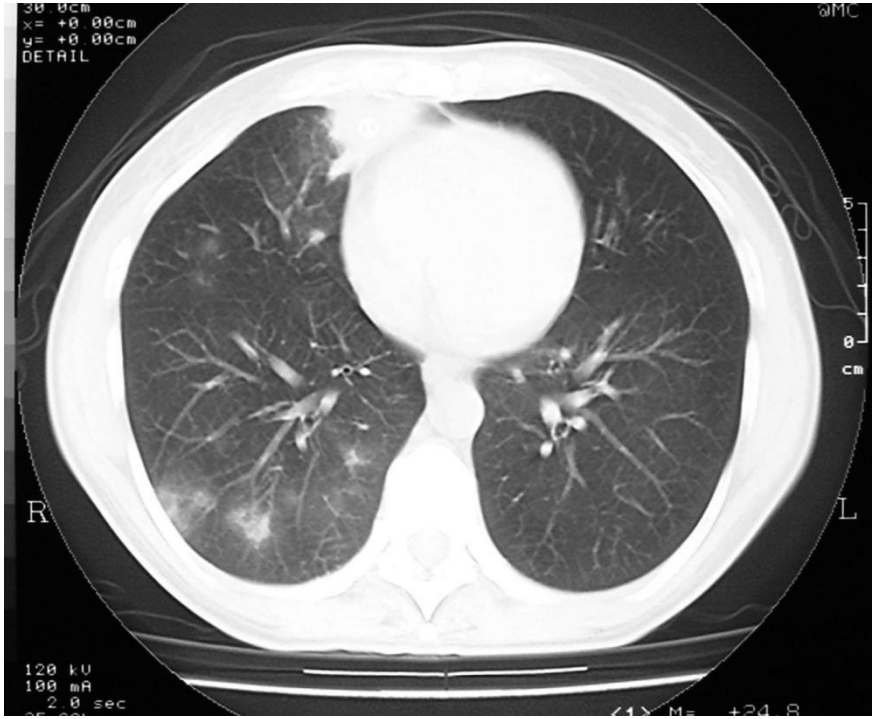
Organizing pneumonia

- OP now 110 incl. ICI
- AFOP now 15 incl. ICI





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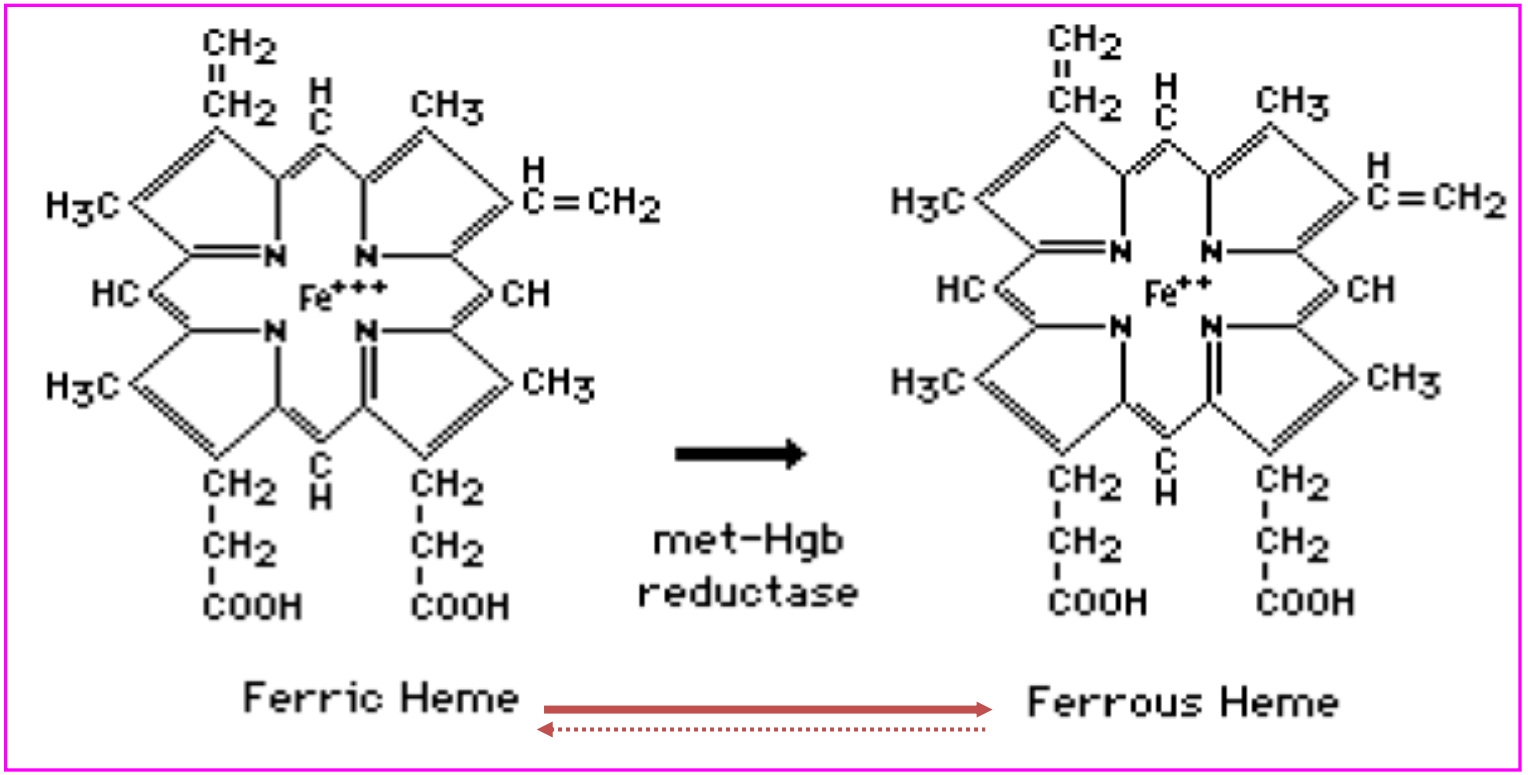
y= +0.00cm
DETAIL
120 kV
100 mA
2.0 sec

DI-Methemoglobinemia

- 1-to-4 of 4 iron in oxidized state Fe+++
- Fully oxidized (4/4) Hb (MetHb) <u>unable</u> to bind and carry oxygen (O_2)



- Benzocaine-dapsone-NO

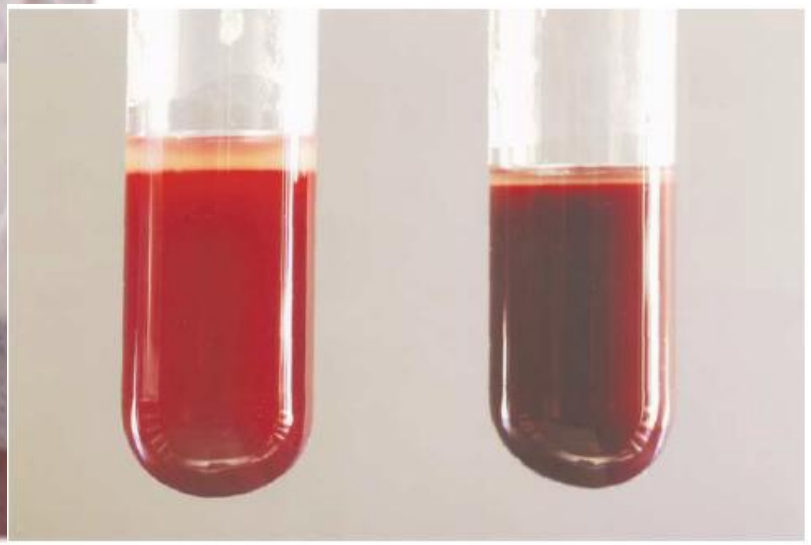


TABLE 1. Known Etiologies of Acquired Methemoglobinemia

Medications
- Benzocaine[100,104] used as a spray: endotracheal intubation[39,72,82,114], transesophageal echocardiography (TEE)[76,109], esophagogastroduodenoscopy (EGD)[1,17,34,35], bronchoscopy[57,62]; used as a topical cream for hemorrhoids or teething preparation[25,30,113]
- Cetacaine[19,24,97,99,116]
- Chloroquine[13,102]
- Dapsone[70,77,87,95,118,119]
- EMLA (Eutectic Mixture of Local Anesthetics) topical anesthetic (lidocaine 2.5% and prilocaine 2.5%)[21,29,110,111]
- Flutamide[46,56,58,98]
- Lidocaine[111]
- Metoclopramide[55,74]
- Nitrates[15,51,68,86]
- Nitric oxide[43]
- Nitroglycerin[8,92]
- Nitroprusside[6,9,106]
- Nitrous oxide[66,69]
- Phenazopyridine (Pyridium)[12,31,81]
- Prilocaine[4,20–22,29,110,111,120]
- Primaquine[13,51,53,90,96,102,103]
- Riluzole[117]
- Silver nitrate[45]
- Sodium nitrate[26,33]
- Sulfonamides (sulfasalazine, sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)[64,77,89,115]

Medical conditions
- Pediatric gastrointestinal infection, sepsis[52,67,88,105]
- Sepsis[59,75,84,104,114]
- Recreational drug overdose with amyl nitrate (a.k.a. ‘‘poppers’’)[79,86]
- Sickle cell crisis[40]

Miscellaneous
- Aniline dyes[23,38]
- Fume inhalation (automobile exhaust, burning of wood and plastics)[54,60,63]
- Herbicides[10,83,108]
- Industrial chemicals: nitrobenzene[37,61], nitroethane (found in nail polish, resins, rubber adhesives)[42,85,101]
- Pesticides[80]
- Petrol octane booster[16]

2000s

- Biological-induced opportunistic infections in RA (TB) Now 1022 papers
- Anti-TNF-induced ILD…
- Targeted agents (TKI)
- Drug-induced systemic reactions
  - Lupus
  - Sarcoid-like
  - GPA, EGPA (+ANCA)
  - Goodpasture (anti-GBM)

Targeted agents

- Afatinib
- Aflibercept
- Alectinib
- Alemtuzumab
- ALK inhibitors
- ATRA
- Anti-PD1-Ab
- Arsenic trioxide
- Azacytidine
- Basiliximab
- Bentuximab
- Bevacizumab
- Bortezomib
- Bosutinib
- Brentuximab vedotin
- Cladribine
- Crizotinib
- Darbepoetin
- Dasatinib
- Denosumab
- Erlotinib
- Everolimus
- Fingolimod
- G- GM-CSF
- Icotinib
- Idelalisib
- Imatinib
- Immune checkpoint Ab
- Interferon alpha, beta
- Ipilimumab
- Lambrolizumab
- mTOR inhibitors
- Matuzumab
- Nilotinib
- Nivolumab
- Obinutuzumab
- Ofatumumab
- Oprelvekin
- Osimertinib
- Panitumumab
- Pemetrexed
- Pomalidomide
- Ponatinib
- Prinomastat
- Raltitrexed
- Ridaforolimus
- Rituximab
- Sirolimus
- Sorafenib
- Sunitinib
- TGN1412
- Tacrolimus
- Temsirolimus
- Temozomolide
- Temsirolimus
- Thalidomide
- Trastuzumab
- TKI
- Vantedanib
- Vemurafenib
- Zotarolimus

Osimertinib

2

Last update 22/11/2017

:

I - Interstitial/parenchymal lung disease

I.a	Pneumonitis (ILD), acute, severe (may occasion an ARDS picture)	1
I.b	Pneumonitis (ILD)	1
I.c	Eosinophilic pneumonia (pulmonary infiltrates and eosinophilia)	1
I.h	Subclinical pulmonary infiltrates/ILD	1

XII - Cardiovascular involvement / toxicity

XII.p	QT prolongation	1
XII.r	Congestive heart failure	1

XV - Pathology

XV.a	Path: Cellular NSIP pattern (see also Ia, Ib)	1
XV.b	Path: Eosinophilic pneumonia (subacute or acute) (see also Ic)	1

I - Interstitial/parenchymal lung disease

I.a	Pneumonitis (ILD), acute (can produce ARDS)	1
I.b	Pneumonitis (ILD)	2
I.d	Organizing pneumonia pattern (an area or areas of consolidation on imaging)	1
I.g	Pulmonary fibrosis (Not otherwise specified)	1
I.l	Diffuse alveolar damage (DAD) (see alsoo under IIb and XVf)	1
I.w	Rapidly progressive ILD/pulmonary fibrosis (Hamman-Rich syndrome)	1
I.ad	Radiation recall pneumonitis	1

II - Pulmonary edema - Acute lung injury - ARDS

II.b	ARDS - Acute lung injury	2

III - Pulmonary/alveolar hemorrhage

III.a	Diffuse alveolar hemorrhage (DAH)	-

V - Pleural and/or pericardial involvement

V.f	Pneumothorax	1

XI - Miscellaneous

XI.w	Cavitation/necrosis of lung tumor or metastases	1

XII - Cardiovascular involvement / toxicity

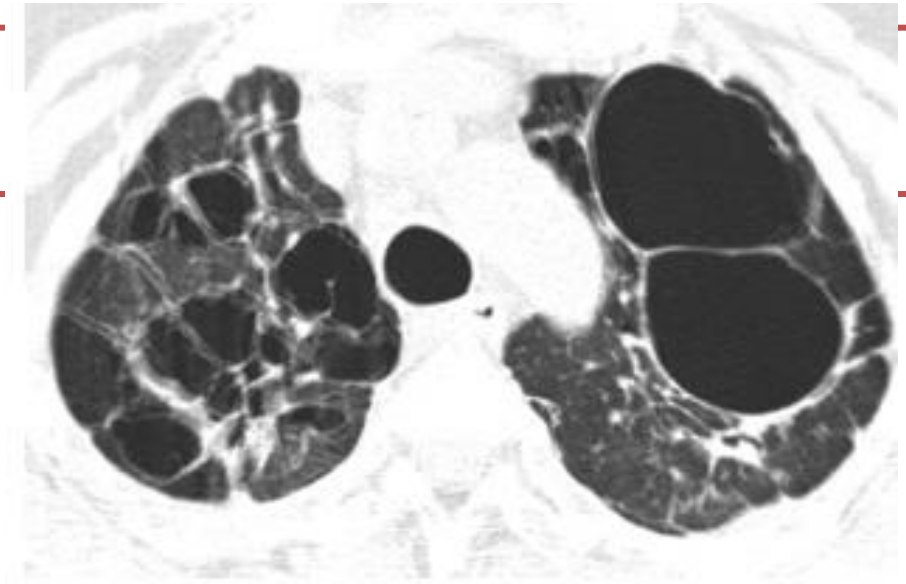
XII.f	Cardiomyopathy (acute, subacute, chronic)	1

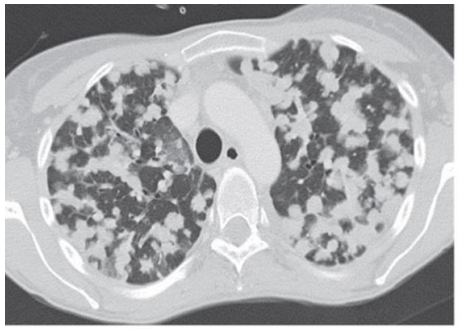
XV - Pulmonary pathology

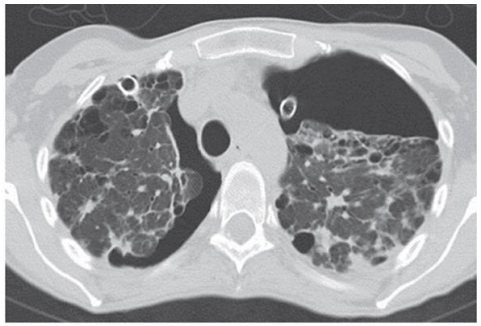
XV.c	Path: Organizing pneumonia (OP/BOOP) pattern (see also Id)	1
XV.f	Path: Diffuse alveolar damage (DAD-pattern) (see also IL)	1

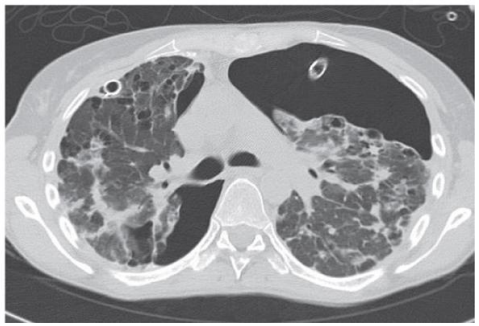
XVI - Imaging

XVI.af	Imaging: Lung cysts or bullae (see also XVI ah/bf)	1
XVI.ay	Imaging: Asymmetrical, predominantly unilateral involvement	1









Bevacizumab

2

No undisputable evidence for bevacizumab-induced ILD as of Oct, 2014

Last update 18/10/2014

:

I - Interstitial/parenchymal lung disease

I.b	Pneumonitis (ILD)	-

II - Pulmonary edema - Acute lung injury - ARDS

II.b	ARDS - Acute lung injury	-

III - Pulmonary/alveolar hemorrhage

III.a	Alveolar hemorrhage, diffuse (DAH)	-
III.c	Hemoptysis	1
III.g	Bleeding/hemorrhage from/around preexisting lung tumor (Localized AH)	2
III.h	Major/massive hemoptysis	1
III.k	Epistaxis	1

IV - Airway involvement

IV.a	Bronchospasm - Wheezing - Asthma	1

V - Pleural and/or pericardial involvement

V.f	Pneumothorax	-

VI - Pulmonary vasculopathies

VI.a	Venous thrombo-embolism - Pulmonary embolism	2
VI.b	Pulmonary arterial hypertension	1

VIII - Central-large-upper airway (incl pharyngeal-nasal) involvement

VIII.o	Perforation of the nasal septum	1
VIII.ab	Tracheal/bronchial fistula	1

X - Systemic conditions, syndromes and reactions

X.f	Anaphylaxis	1
X.s	Vasculitis, pulmonary/systemic (ANCA-positive)	-

VIII - Central-large-upper airway (incl pharyngeal-nasal) involvement

VIII.o	Perforation of the nasal septum	1
VIII.ab	Tracheal/bronchial fistula	1

X - Systemic conditions, syndromes and reactions

X.f	Anaphylaxis	1
X.s	Vasculitis, pulmonary/systemic (ANCA-positive)	-

XI - Miscellaneous

XI.w	Cavitation/necrosis of lung tumor or metastases	1

XII - Cardiovascular involvement / toxicity

XII.a	Left ventricular dysfunction/failure	1
XII.e	Takotsubo (stress) cardiomyopathy	1
XII.g	Myocardial ischemia/infarction - Coronary artery disease, acute	1
XII.ai	Cardiotoxicity	2
XII.at	Aortitis	1

XVI - Imaging

XVI.ab	Imaging: Cavitating lung nodule or nodules (see also Iq, XIs, XIIi, XVIaa and XVIIp)	1
XVI.af	Imaging: Lung cysts or bullae (see also XVI ah/bf)	1
XVI.bf	Imaging: Tumoral cavitation	1

- Dasatinib

I - Interstitial/parenchymal lung disease

I.b	Pneumonitis (ILD)	2
I.d	Organizing pneumonia pattern (an area or areas of consolidation on imaging)	1
I.n	Pulmonary alveolar proteinosis (PAP)	1
I.y	Progression, acceleration or exacerbation of preexisting ILD/fibrosis	1

V - Pleural and/or pericardial involvement

V.a	Pleural effusion	5
V.c	Pleural thickening	1
V.d	Pleural/pericardial effusion, ANA positive (DI lupus)	1
V.h	Chylothorax	1
V.i	Pleuritis (may cause acute chest pain (see also under XIc)	1
V.m	Pleuropericardial effusion (ANA unknown or negative)	2

VI - Pulmonary vasculopathies

VI.b	Pulmonary arterial hypertension	2

X - Systemic conditions, syndromes and reactions

X.r	Fluid retention	2

XI - Miscellaneous

XI.b	Noncardiac chest pain (acute or subacute). Lone or prominent	1

XII - Cardiovascular involvement / toxicity

XII.c	Pericarditis - Pericardial effusion - Tamponade	3

XV - Pathology

XV.c	Path: Organizing pneumonia (OP/BOOP) pattern (see also Id)	1
XV.n	Path: Pulmonary alveolar proteinosis pattern (PAP pattern)	1
XV.ao	Path: Pleuritis, pleural fibrosis	1
XV.ch	Path: Organizing fibrinous pleuritis (OFP)	1

XVI - Imaging

XVI.m	Imaging: Interlobular septal thickening	1
XVI.an	Imaging: Pleural effusion	2

SEE ALSO UNDER

- Bosutinib 2
- Imatinib 3
- Ponatinib 2

DI AI systemic reactions

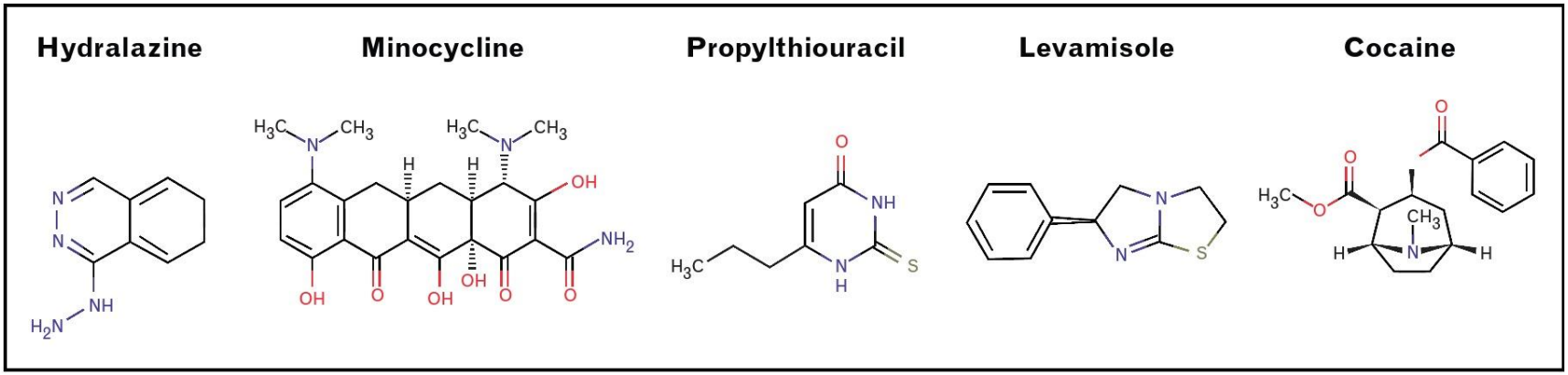


FIGURE 1. Chemical structures of hydralazine, minocycline, propylthiouracil (PTU), levamisole and cocaine. There is a paucity of information regarding structural similarities and differences of these compounds in the literature; therefore, they are represented here for visual review (created using DrugBank).

	Hydralazine	Minocycline	PTU	Levamisole-adulterated cocaine
ANCA serotype	MPO-ANCA	MPO-ANCA	MPO-ANCA	MPO-ANCA and PR3-ANCA
ANCA IF pattern	Perinuclear	Perinuclear	Perinuclear	Perinuclear
MPO-ANCA and PR3-ANCA double positivity	Rare	Rare	Rare	Very common

Nontherapy drugs

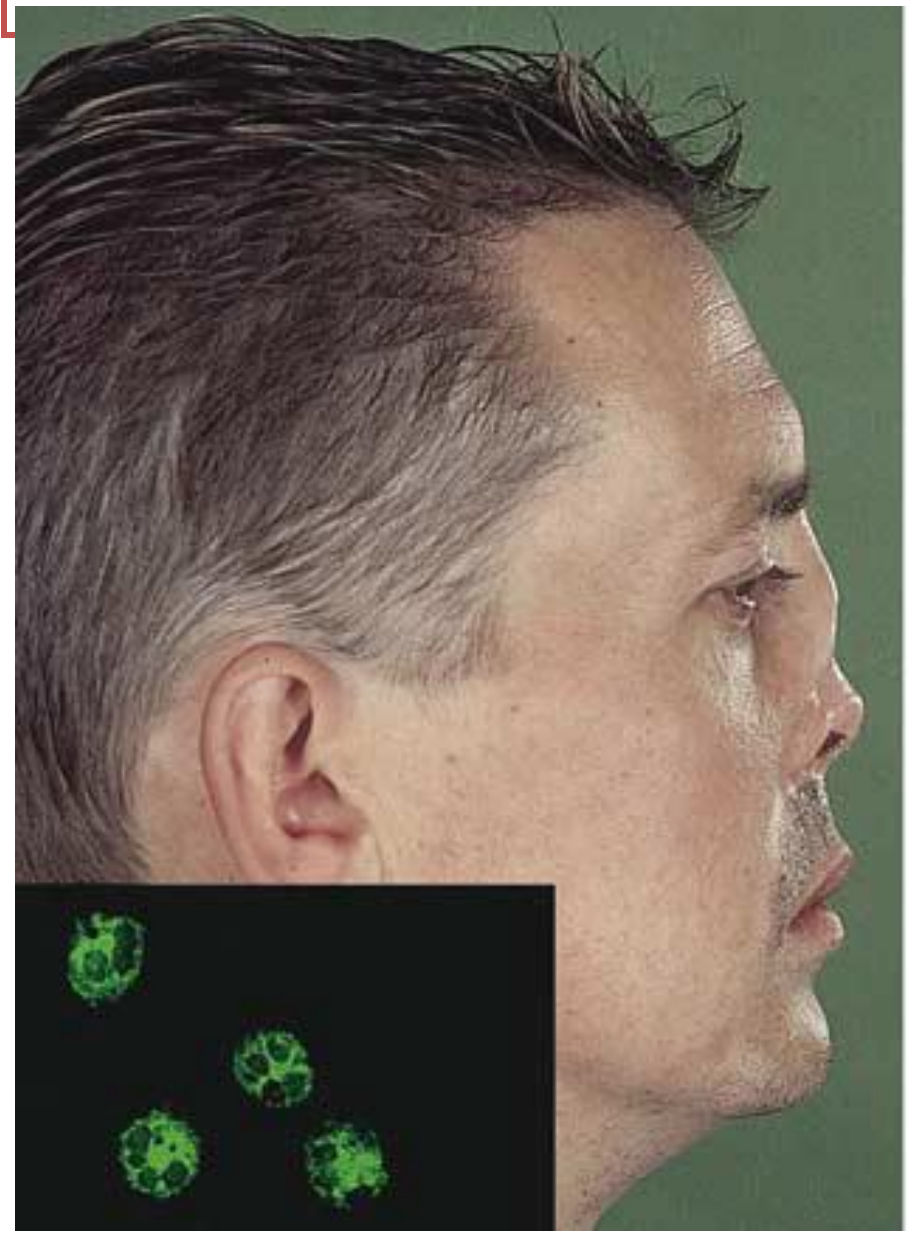
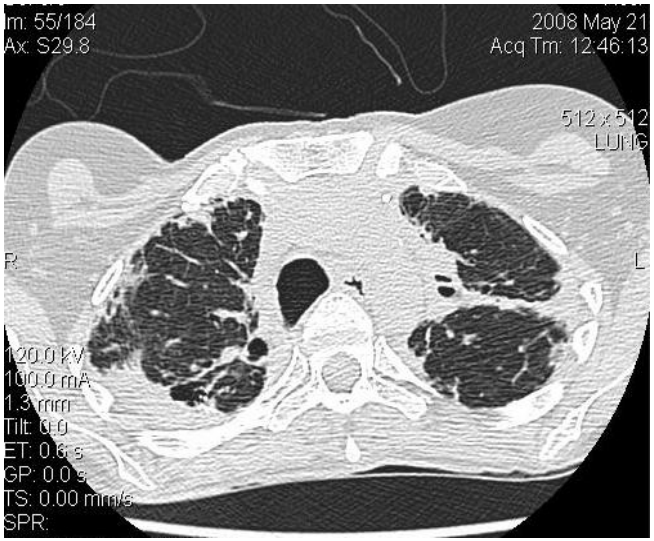


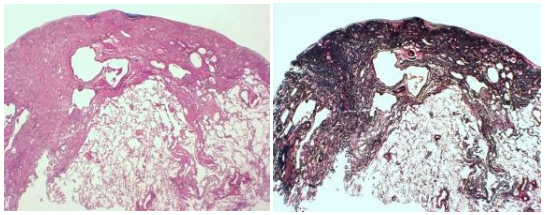
Fig 1. Clinical presentation of patient shows bilateral collapse of ala.

Fig 2. Palatal defect after loss of maxillary sinuses, ethmoid sinuses, turbinates, and nasal septum. Note unaffected maxillary alveolus.

2010s

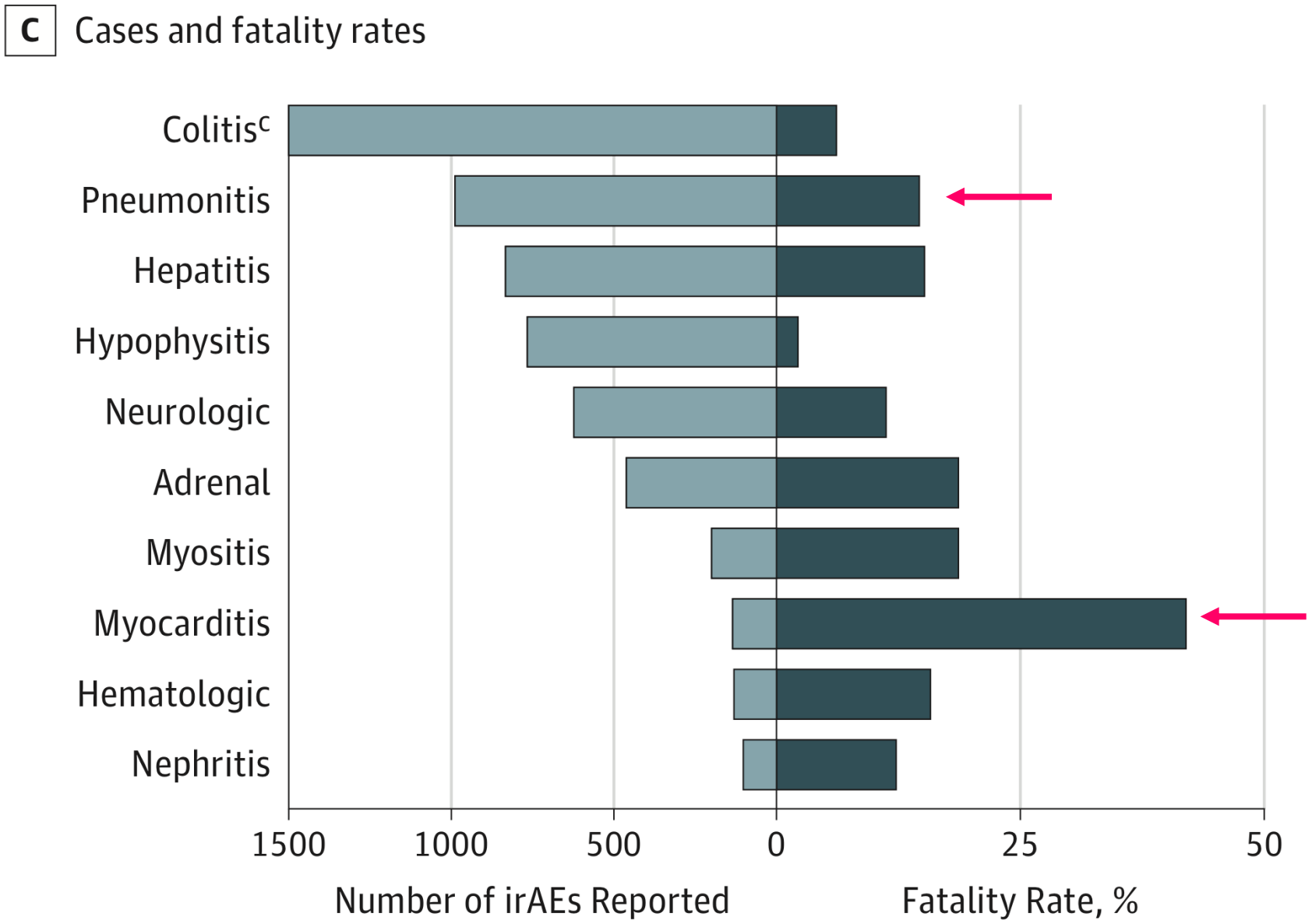
- Direct anticoagulant-induced
  - Bleeding
  - Acute ILD
- Direct-acting antiviral agents & ILD
- DI PPFE





ICI-related lung injury

Wang *et al*. 2018



IRP: Clinical profile

- Class effect
- Easily dismissed as disease progression, an infection, or incidental ILD
- Can progress rapidly and become life-threatening or lethal if not managed properly
- Cause of treatment-related death
  - NSCLC (Chuzi, 2017)
  - 4/43 (Naidoo, 2017)
- Watchful vigilance/early Dg encouraged
- Most cases respond to CST
- Watch AEs in other organs

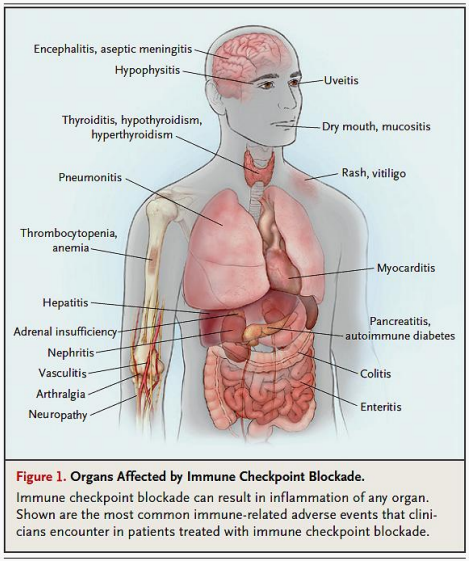


Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

IRP: Incidence (El-Osta, 2017)

irAE (any grade)	CTLA-4	PD-1	PD-L1	PD-1 + CTLA-4	PD-L1 + CTLA-4
	4783	5176	790	462	117
Diarrhea	31.80%	10.50%	4.40%	42.90%	29.90%
Colitis	7.70%	0.80%	1.10%	13.90%	12.10%
Pruritus	22.00%	11.10%	6.70%	35.10%	20.50%
Rash	24.40%	12.80%	7.20%	45.20%	14.50%
Vitiligo	0.60%	3.70%	NR[a]	8.00%	NR
Hypophysitis	5.40%	0.30%	NR	8.00%	NR
Hypothyroidism	2.90%	5.50%	4.30%	13.90%	10.30%
Hyperthyroidism	0.40%	2.10%	2.30%	7.60%	NR
Pneumonitis	0.30%	2.60%	2.30%	7.10%	5.10%
Increased ALT	4.50%	2.20%	2.60%	18.80%	10.10%
Increased AST	4.70%	2.10%	2.70%	17.10%	7.70%
Increased lipase	0.30%	0.30%	NR	4.80%	12.10%

[a] Not Reported.

OR Combo 2.04-2.86 Nishino, 2016
Real world ~10%

Time to onset

- Mean delay: 2.8 mo (9 days – 19.2 - 24 months)
- Shorter if severe and/or with combo therapy
- Window for lung damage can be longer than actual period of exposure

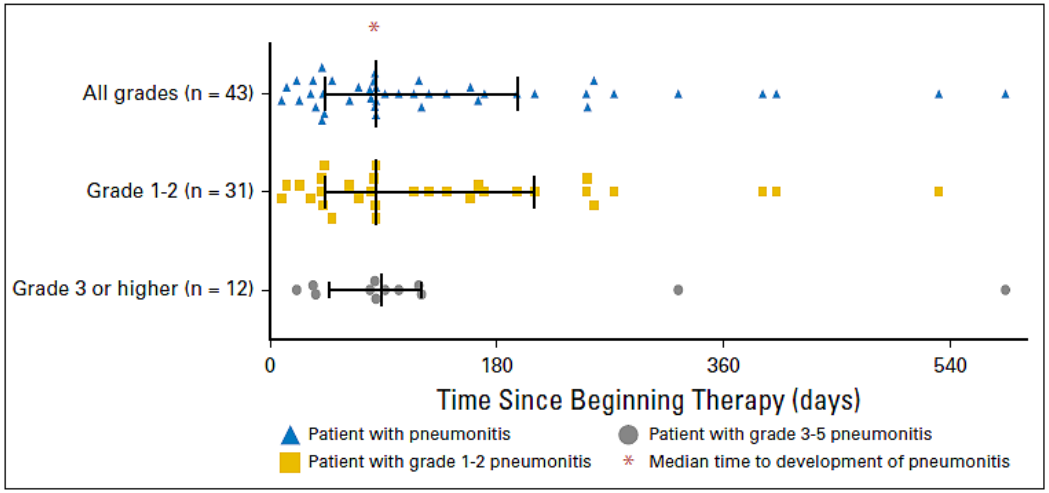


Fig 1. Time from first dose of anti–programmed death-1/programmed death ligand 1 therapy to date of pneumonitis event stratified by grade, with interquartile range and median values shown.

- Very late
- Delayed

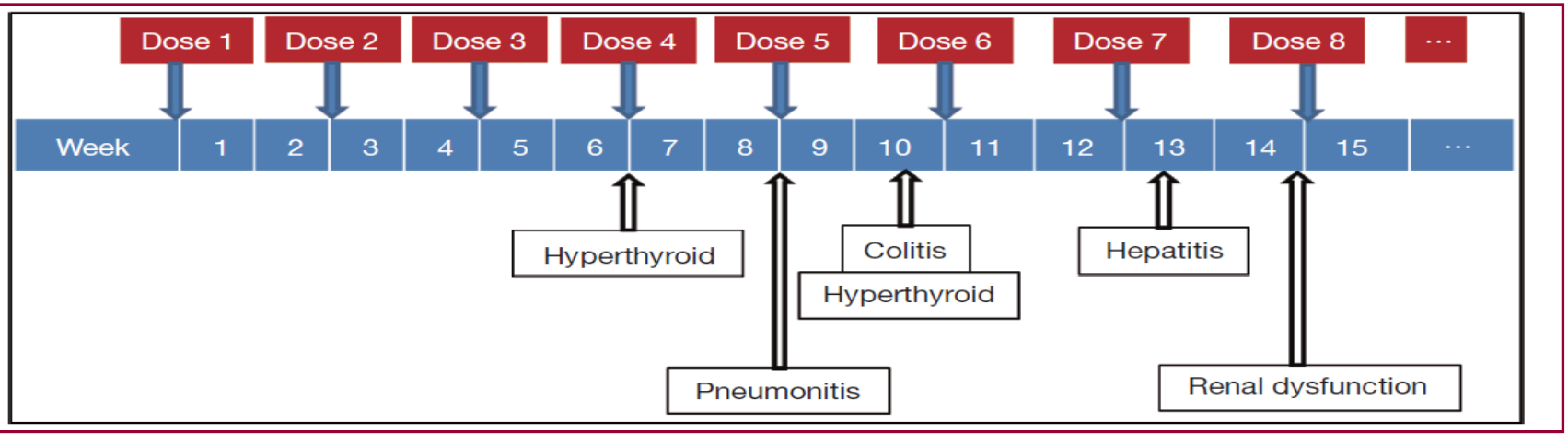


Figure 2 Median time for appearance of immune-related adverse events (irAEs) with nivolumab based on a phase III study (9).

Risk factors

- Dose (CTLA4 – ?PD-1 PD-L1)
- Combination IT
- In lung cancer
  - Squamous histology (Khunger, 2017)
  - Being treatment-naive (4.3% *v*. 2.8%; p<.03) (Khunger, 2017)
  - Prior radiation to the chest: 33.9% *v*. 24.8% (Antonia, 2017)
  - Hx of RILI: 26.5% *v*. 9.6% (Tamiya, 2017)
  - Preexisting ILD/IPF
    - Kanai 2018: 31%/12% v. 19%/5%

Clinical presentation

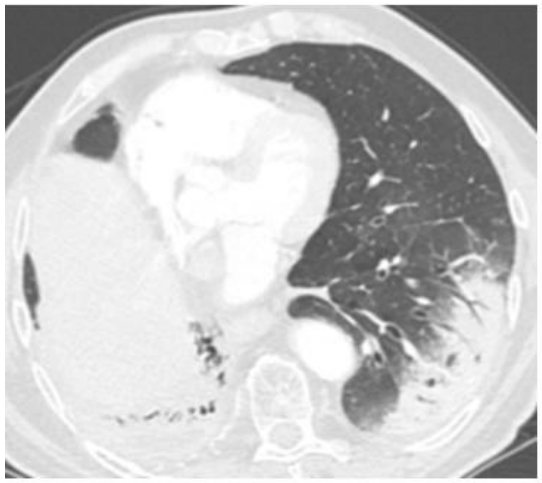
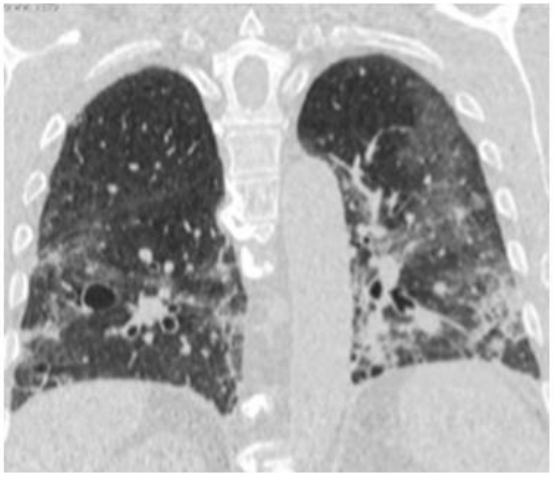
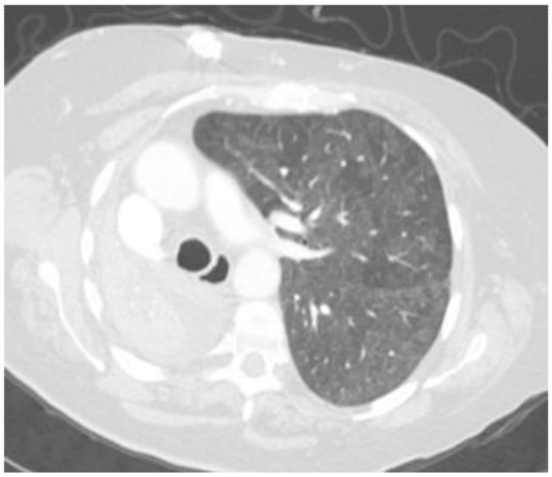
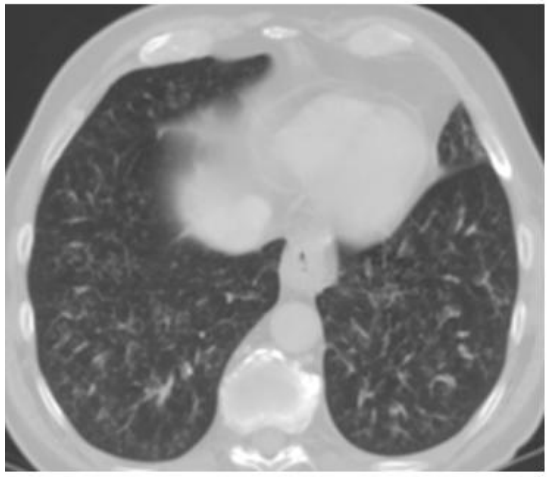
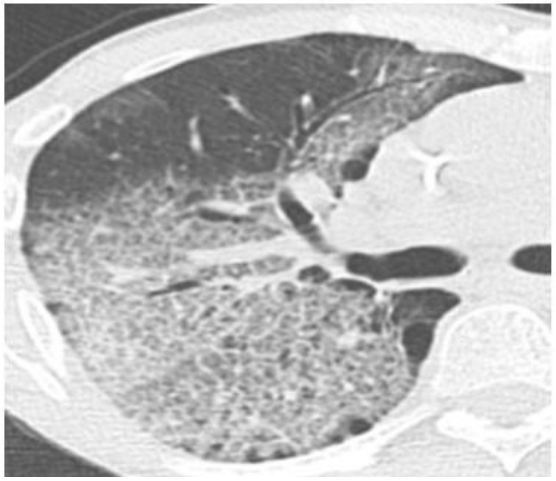
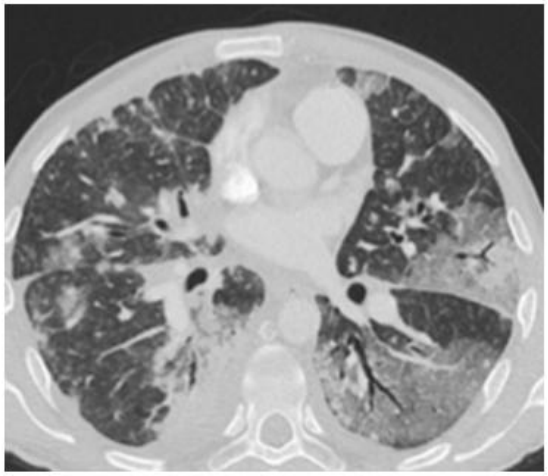
- Pulm. infiltrates and the asymptomatic state 25-30%
- Unresolving dyspnea: 53%
- Cough (usually dry): 35%
- Fever (low-grade): 12%
- Chest pain (unusual): 7%
- Low SpO2 (Grade 3-4 in ~33%)
  - May progress rapidly
- T-cell immune response considered not tissue specific
- irAE in distant organ(s) ~50%

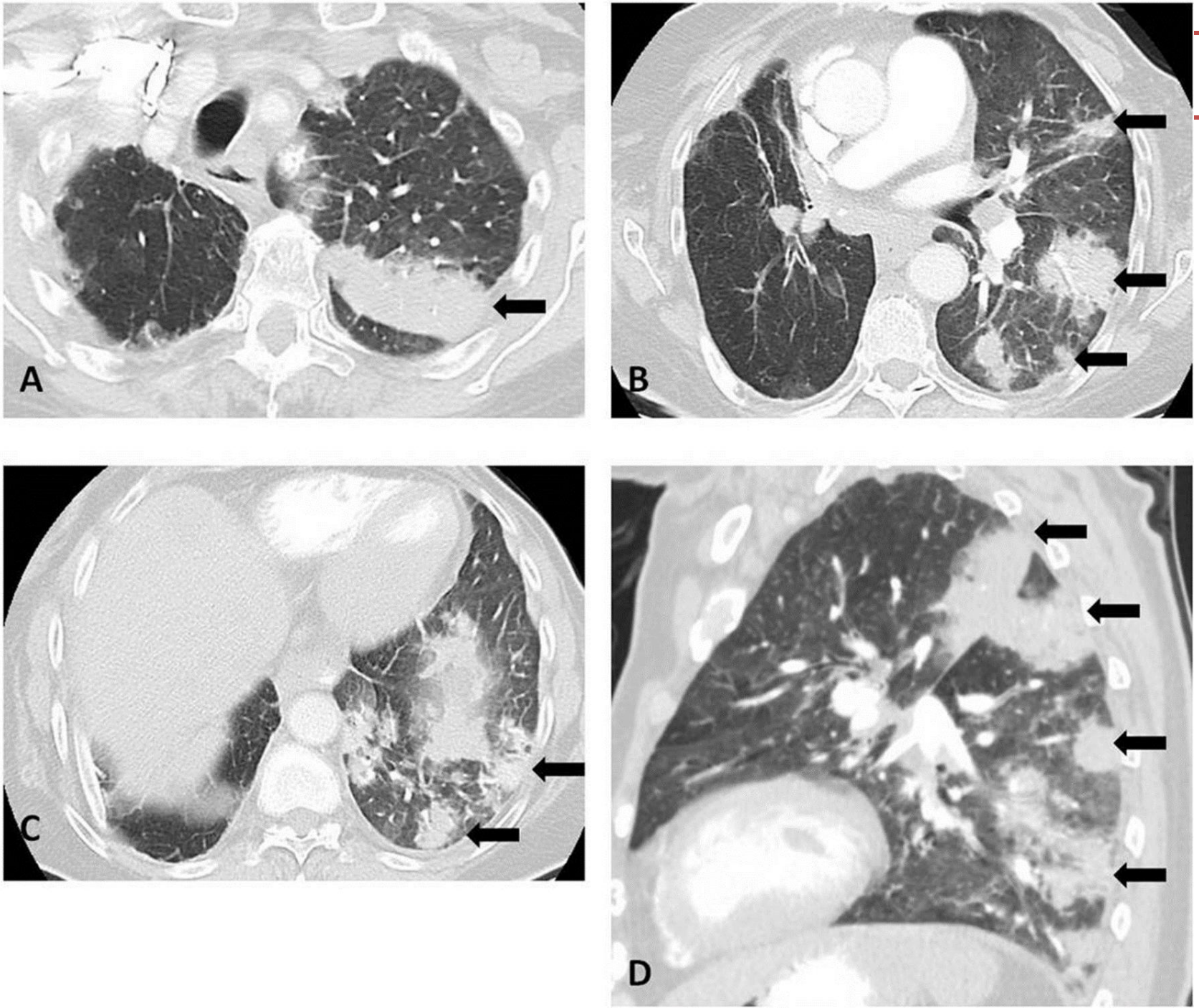
Imaging

- CXR may miss >25% of cases - CT referred
- Measure overall tumor burden (irRC)
- Ground-glass: 10/27 [37%] (Naidoo 2016)
- Mosaic attenuation HSP-like: 6/27 [22%]
- Consolidation & air bronchograms OP-like : 5/27 [19%]
  - May be more common in lung cancer patients
  - May require CST more often
- Reticular interstitial opacities : 2/27 [7%]
- Lobar involvement
- Unclassifiable : 4/27 [15%]

- Extent (will help guide steroid therapy)
  - Mild 15/27 [56%]
  - Moderate 6/27 [22%]
  - Diffuse 6/27 [22%]
- Radiologic subtypes more often consistent throughout a patient’s clinical course

Delaunay *et al*. 2017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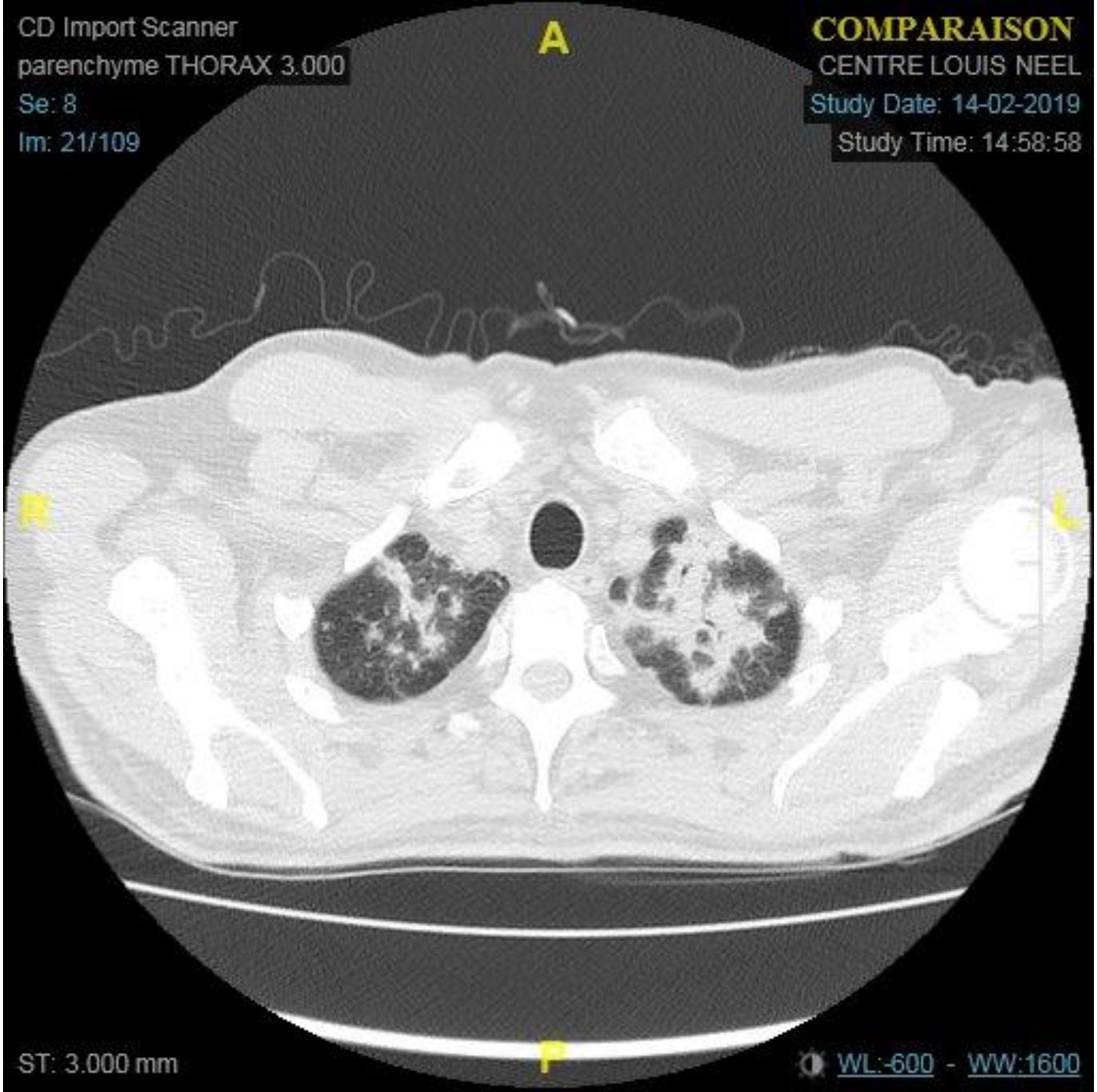
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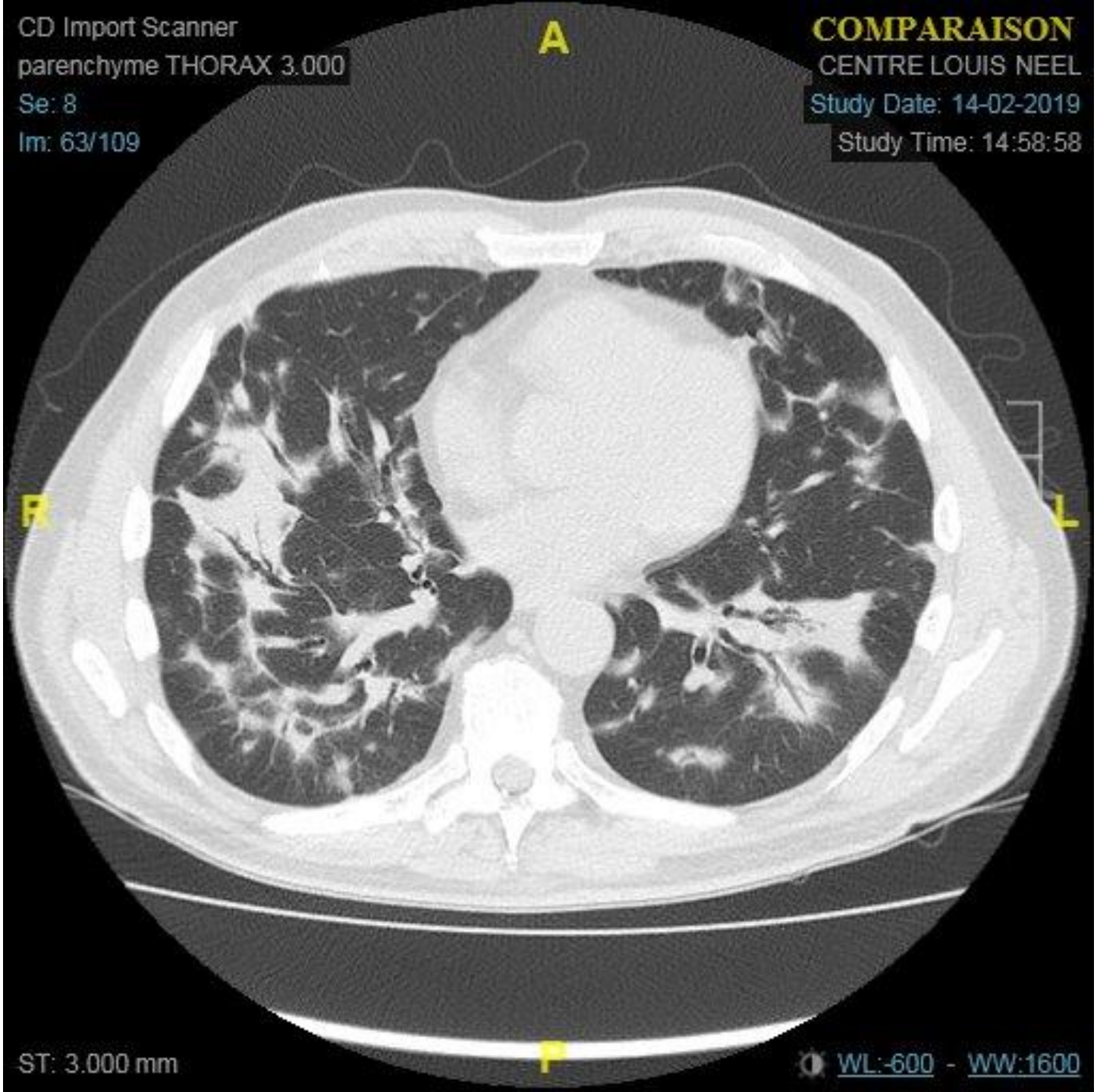
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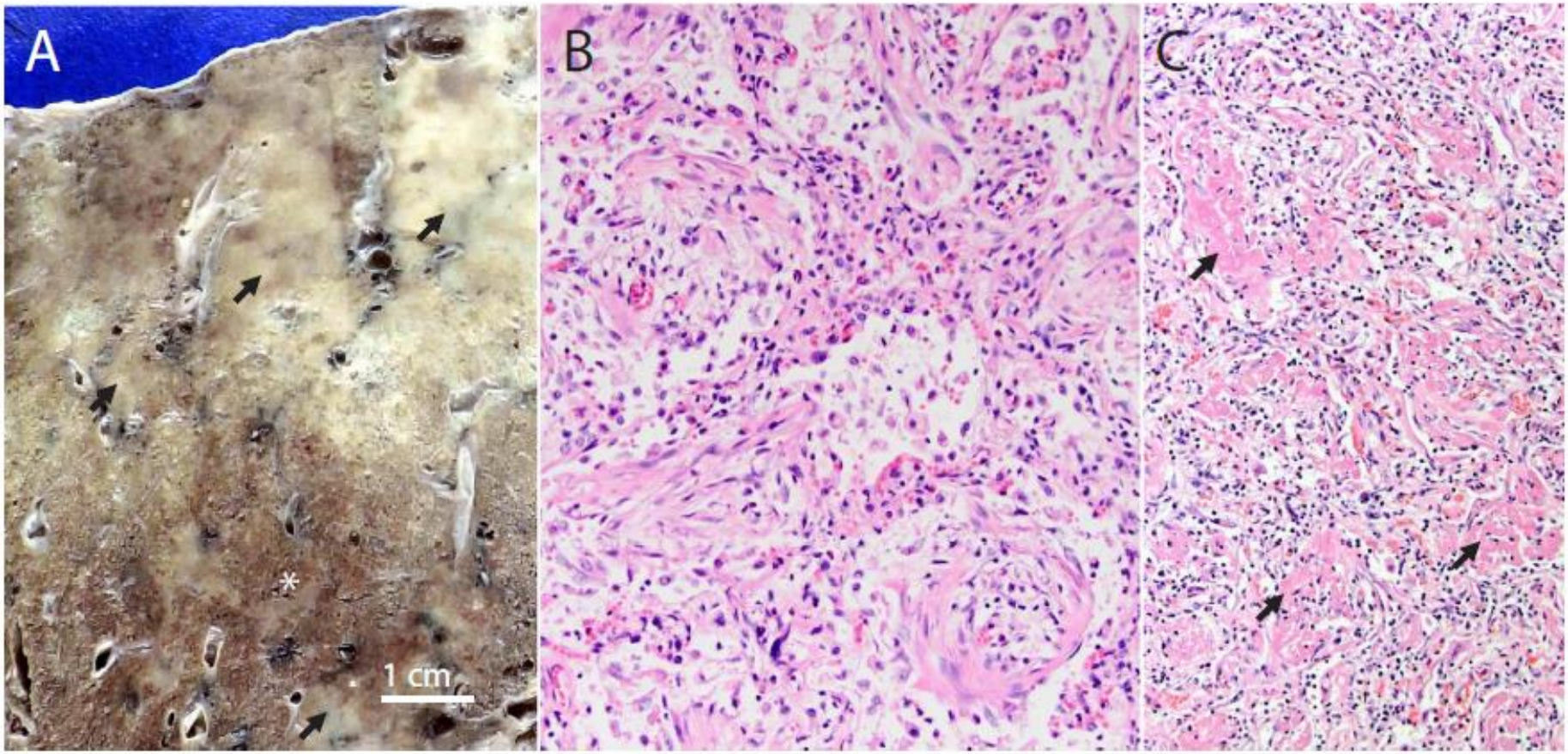


Fig. 3. Autopsy findings. A. Fixed lung sections demonstrate multifocal consolidations (arrows) with only focal areas of grossly uninvolved lung parenchyma (asterisk). B. These consolidations correspond to a histopathologic organizing pneumonia pattern. C. Patchy areas of acute lung injury with airspace fibrin (arrows) were identified.

Bronchoalveolar lavage cell data: review

Author	Ly	CD4+/CD8+	PMN	Comment
Fragkou 2016 P	28,7%	0,4	NS	
Sehgal, 2016 P	5%	CD4>CD8 in mucsa	39%	Eos 2% Pathology: CD4
Brahmandam, 2017 N				Unremarkable
Diamantopoulos, 2017 N	Predominant			
Ishiwata, 2017 N	53%		30%	
Franzen, 2017 I	‘Lymphocytosis’			
Oda, 2018 P/P	29%/36%	1,0/1,9		TIM3/PDL1

Pathology

- Naidoo *et al*. 2017
- 11/27 patients at MSKCC
  - Cellular interstitial pneumonia (NSIP): 4
  - OP: 3
  - DAD: 1
  - Poorly formed granulomas: 3
  - Eosinophilic infiltrate: 2

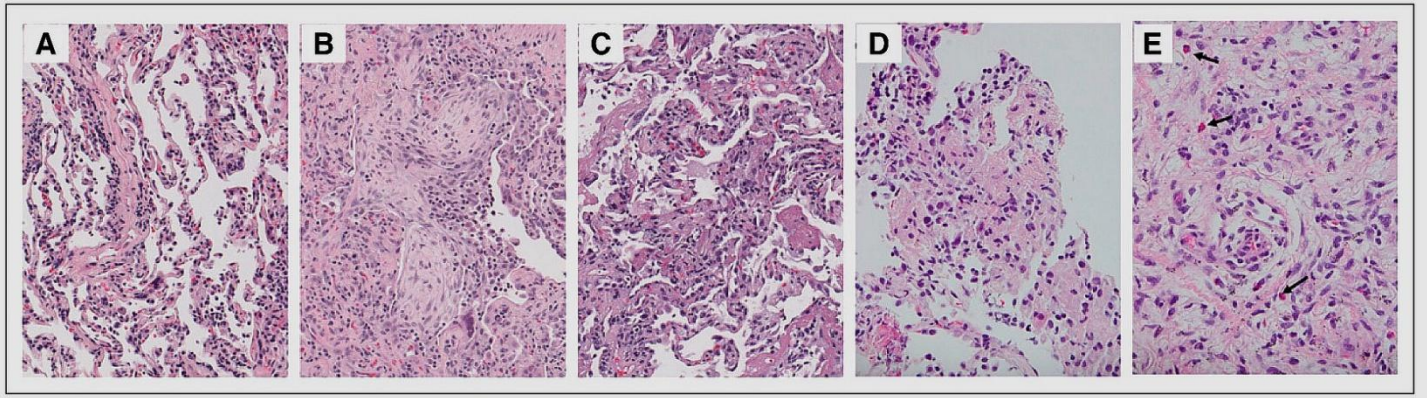


Fig A2. Histologic patterns of pneumonitis associated with anti–programmed death-1/programmed death ligand 1 therapy on lung biopsy (hematoxylin and eosin [HE] stain magnification, ×200) included (A) cellular interstitial pneumonitis (mild case shown), (B) organizing pneumonia, and (C) diffuse alveolar damage. Additional findings (HE stain magnification, ×400) include (D) poorly formed granulomas, and (E) eosinophils (arrows).

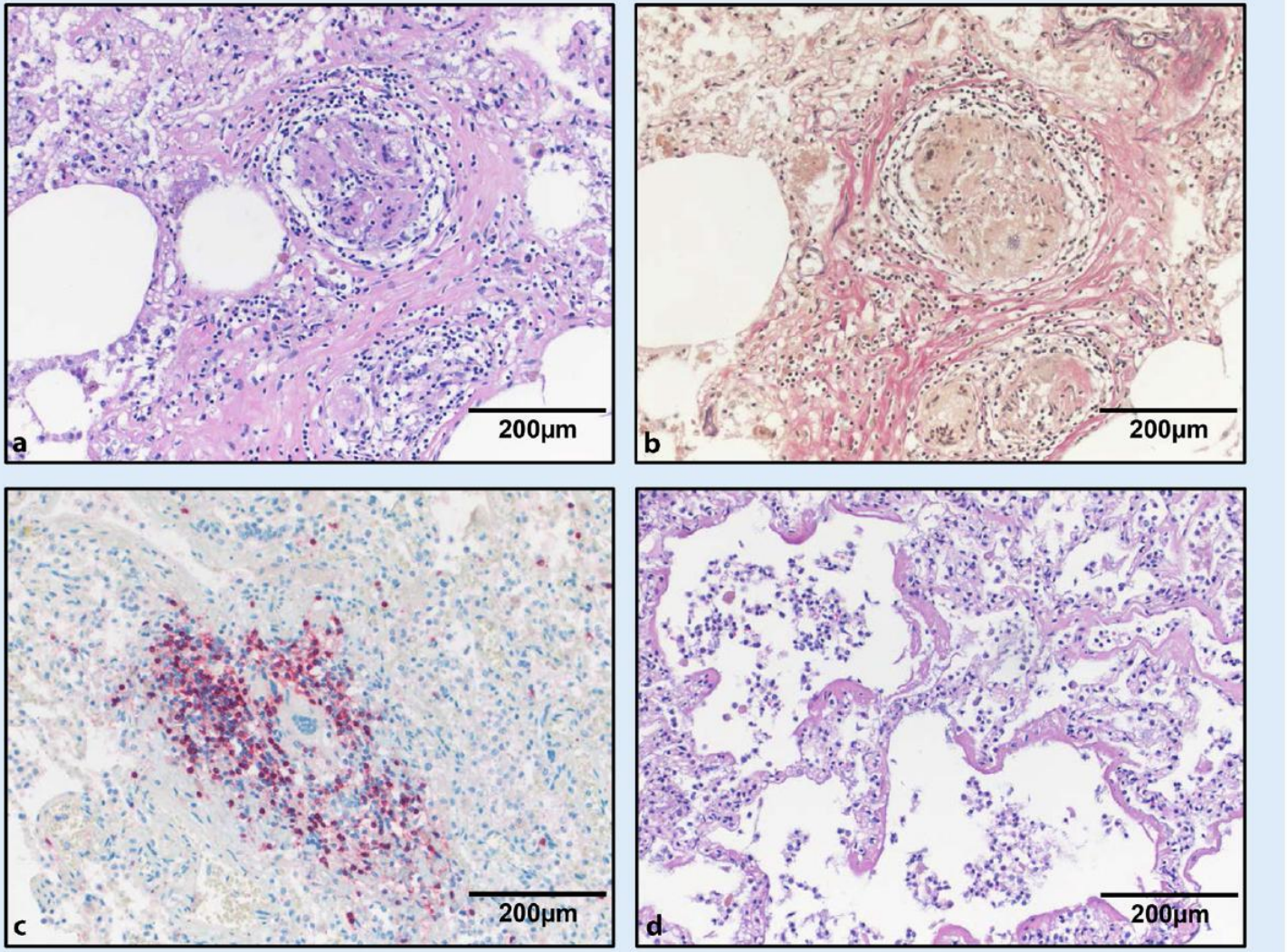


Abb. 3 ◄ ICI-induzierte Schädigungsmuster der Lunge. **a–c** *Sarkoid-like reaction* der Lunge. 35-jährige Patientin mit metastasiertem Melanom nach sequenzieller Therapie mit Ipilimumab und Nivolumab. Keine vorbekannte Pneumopathie. Autopsiebefund der Lunge mit septalen epitheloidzelligen und riesenzellhaltigen Granulomen mit interlobulärer, peribronchialer und subpleuraler Verteilung (**a**, H.E.-Färbung). Deutlicher fibrotischer Ring in der Elastica-van-Gieson-Färbung (**b**). Immunhistochemischer Nachweis zahlreicher intra- und perigranulomatöser CD8-positiver T-Zellen (**c**). **d** Diffuser Alveolarwandschaden mit Ausbildung hyaliner Membranen. Ebenfalls Autopsiebefund der Lunge dieser 35-jährigen Patientin mit metastasiertem Melanom. H.E.-Färbung

- Concomitant involvement of heart, CNS, liver, bone marrow

- Velez, 2017
- Nine asymptomatic patients
- Received neoadjuvant anti-PD1
- Surgery for lung cancer
- PCR & stains negative
- Pathology specimen away from the tumor
- Compared to the 11 just mentioned Memorial cases

2003 Pathologic Patterns of Inflammatory Lung Injury Following Anti-PD-1 Immunotherapy in Asymptomatic Patients

Moises J Velez, Charles Leduc, Matthew Hellmann, Jamie Chaft, Jarushka Naidoo, Janis M Taube, Patrick M Forde, Valerie Rusch, William Travis, Natasha Rekhtman.
Memorial Sloan Kettering Cancer Center, New York, NY; The Johns Hopkins University, Baltimore, MD.

Background: PD-1/PD-L1 immune checkpoint blockade is an emerging treatment option for many cancers and works by potentiating the host immune response against tumor. Pneumonitis is an uncommon but recognized immune-related adverse event (irAE) associated with anti-PD-1/PD-L1 agents, with clinical manifestations ranging from asymptomatic to fatal. We examined the histopathologic findings in the non-tumor lung tissue of a series of patients following pre-operative anti-PD-1 treatment, and compared the findings to those in patients with lung samples obtained for clinically evident PD-1-related pneumonitis.

Design: We evaluated the nonneoplastic lung in 9 patients who underwent surgical resection following pre-operative anti-PD-1 treatment for non-small cell lung cancer. The histologic findings were compared with biopsy or surgical specimens from 11 patients with clinically evident pneumonitis associated with anti-PD-1/PD-L1 therapy recently reported from our institution (Naidoo et al. J Clin Oncol. 2016 PMID: 27646942).

Results: All 9 patients who received pre-operative anti-PD-1 had pathologic evidence of inflammatory injury in the non-neoplastic lung, including organizing pneumonia (n=1), cellular interstitial pneumonia (CIP) (n=3, one also with non-necrotizing granulomas), necrotizing granulomatous inflammation (n=1), non-necrotizing granulomatous inflammation (n=2) and non-specific chronic inflammation (n=2). There was no evidence of infection in any samples based on special stains, cultures and viral PCR, when available. Of these 9 patients, only one (with CIP) had clinical evidence of pneumonitis prior to surgical resection. These findings were similar in the phenotypic spectrum and severity to those in 11 recently reported patients with known, clinically recognized pneumonitis with the exception that diffuse alveolar damage was identified only in those with known pneumonitis.

Conclusion: The patterns of lung injury in asymptomatic patients treated with anti-PD-1 are highly varied, and the findings are etiologically non-specific. Nevertheless, the lack of other apparent etiology and the overall similarity of the findings to those in symptomatic patients makes it likely that the observed inflammatory lesions represent subclinical irAE. The clinical significance of this potentially common feature of PD-1 blockade will require further study.

- Inflammatory injury in all 9 patients
  - OP (n=1)
  - Cellular interstitial pneumonia (n=3)
    - one also with non-necrotizing granulomas)
  - Non-necrotizing granulomatous inflammation (n=2)
  - Necrotizing granulomatous inflammation (n=1)
  - Non-specific chronic inflammation (n=2)
- Phenotypic spectrum similar to evident/overt pneumonitis except DAD

Variants

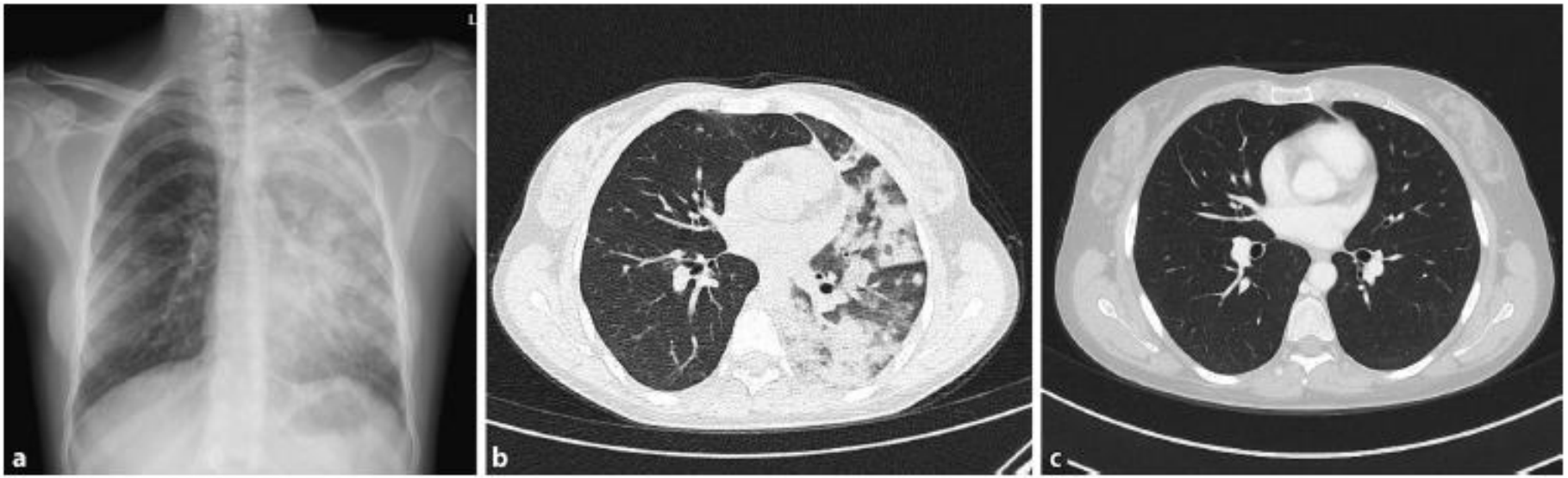
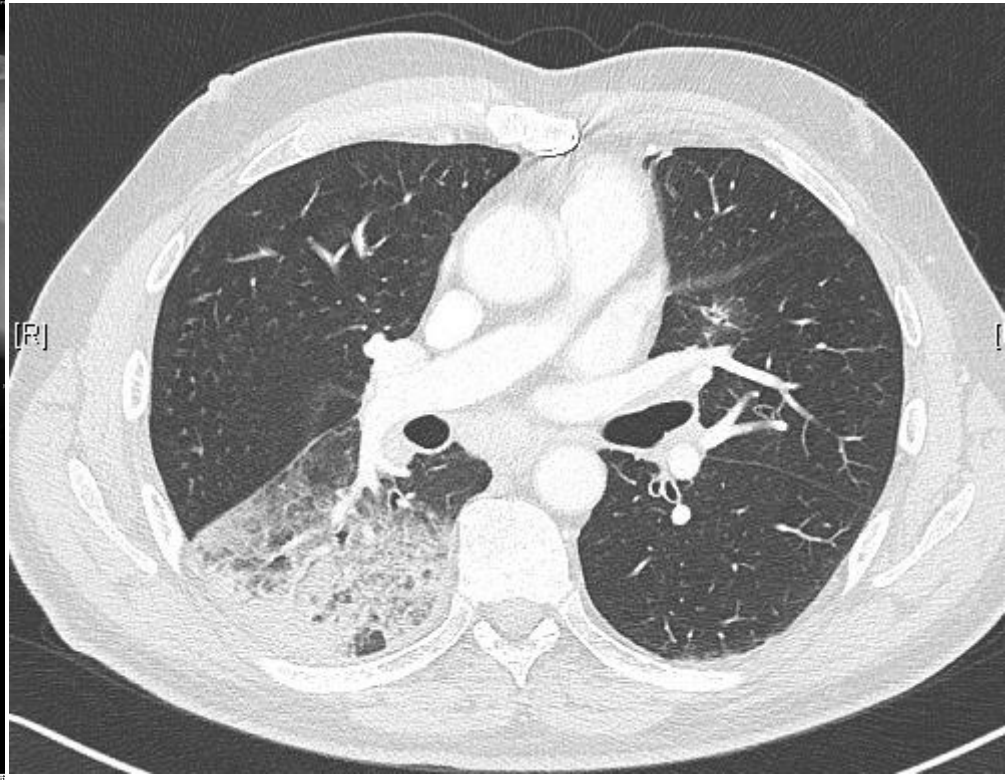
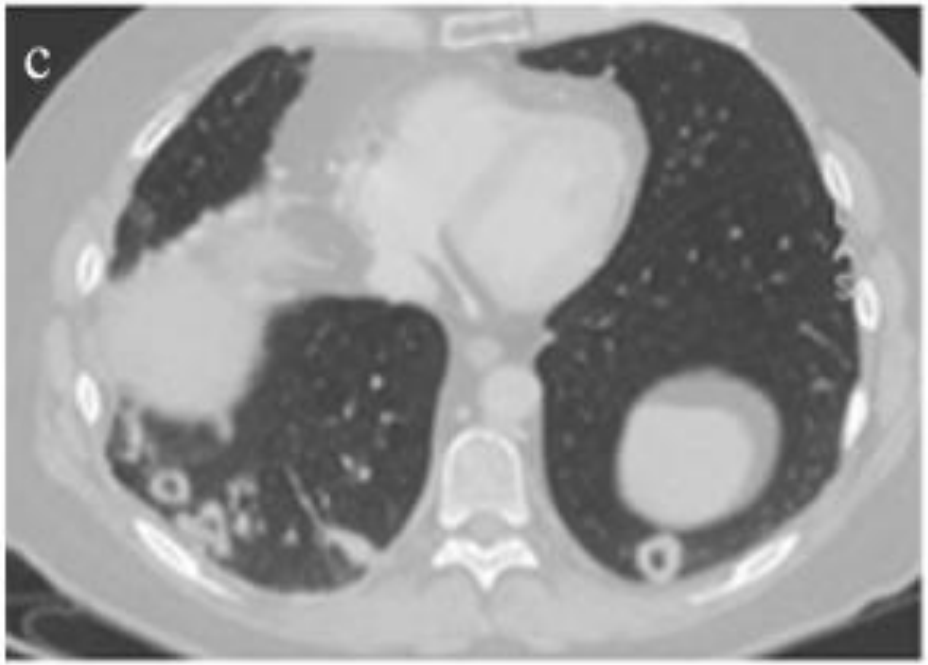


Abb. 2 ▲ Ausgedehnte Pneumonitis in der Röntgenübersichtsaufnahme (**a**) sowie in der Transversalebene eines nativen CT des Thorax (**b**). Nach Therapie mit systemischen Steroiden kam es zu einer vollständigen Rückbildung (**c**). Die Patientin erhielt zuvor Nivolumab im Rahmen einer Studie zur Erstlinienbehandlung eines klassischen Hodgkin-Lymphoms

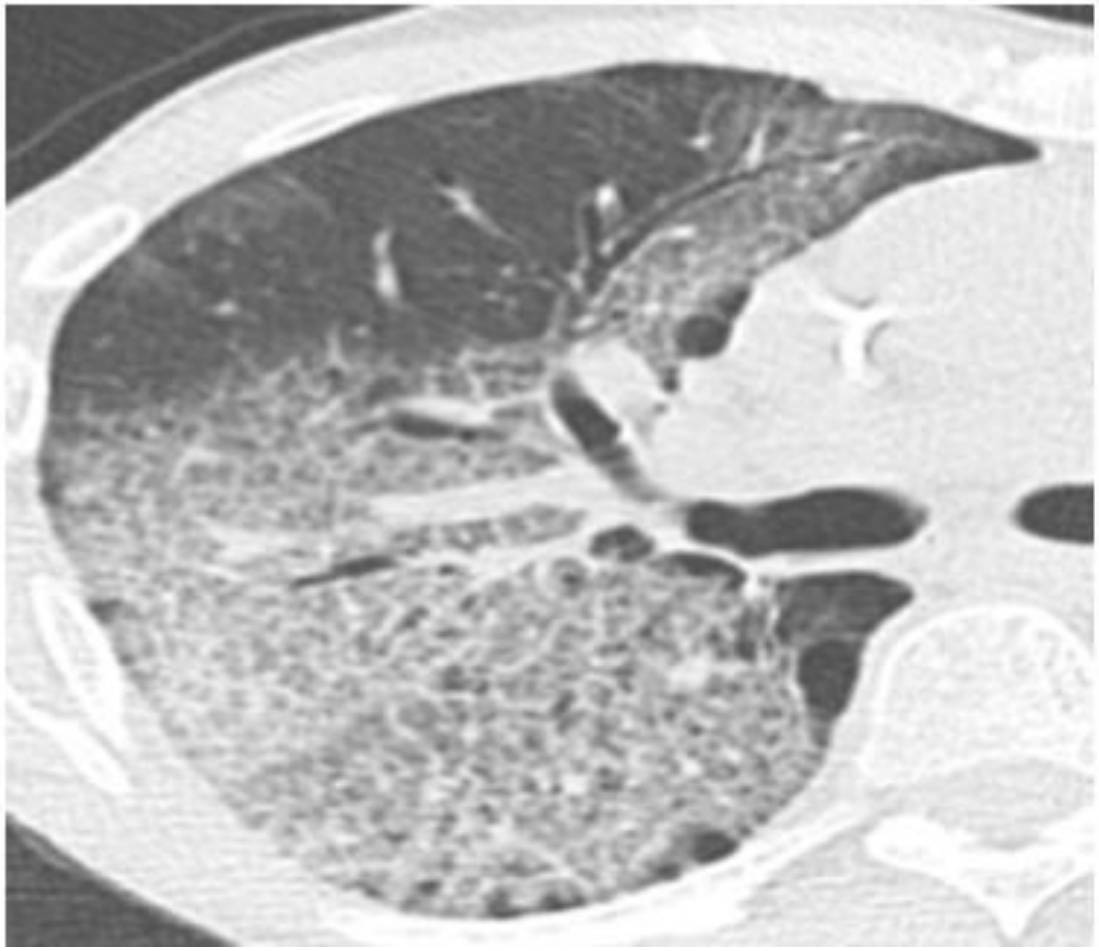
- Lobar infiltrate
- May not cross fissures
- Contrasting with RILI



- Halo - Interlobular thickening



- Intralobular thickening



The Journal of Critical Care Medicine 2017;3(2):84-88

CASE REPORT

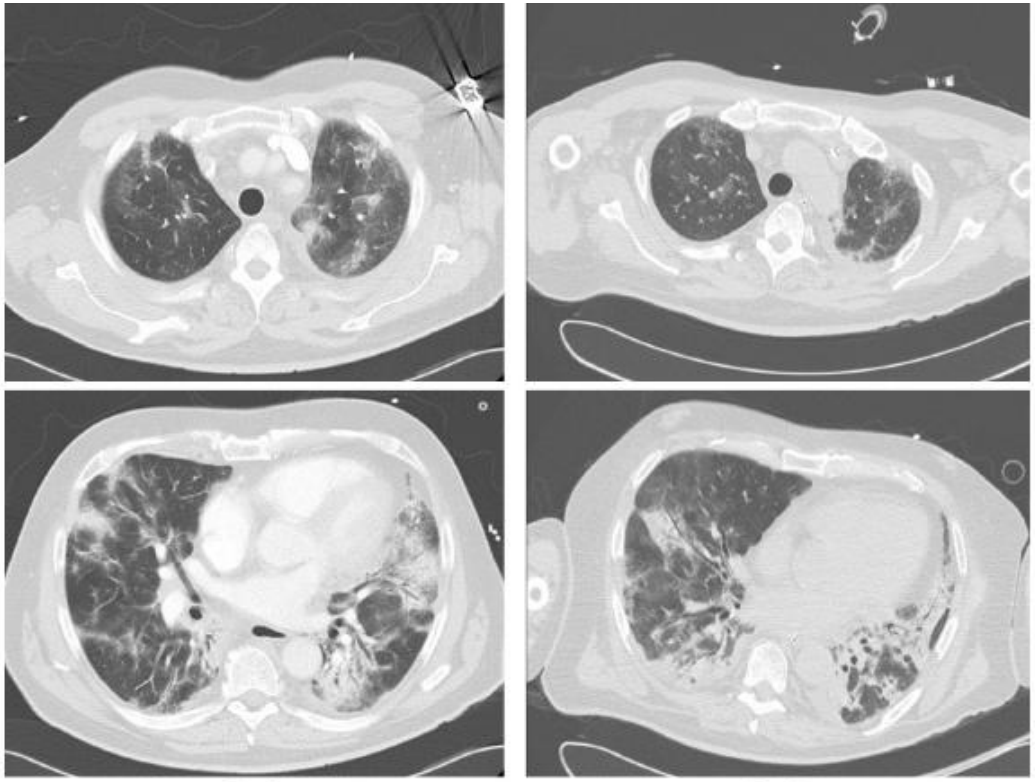
DOI: 10.1515/jccm-2017-0013

Extracorporeal Membrane Oxygenation in Nivolumab Associated Pneumonitis

Thomas-Michael Schneider[1*], Friederike Klenner[2], Franz Brettner[1]

[1] Department of Intensive Care Medicine, Krankenhaus Barmherzige Brueder, Munich, Germany

[2] Department of Internal Medicine V, University of Munich, Germany



Day 1 Day 17

Fig. 1. CT-Scan, with contrast agent, on admission (left side) and high-resolution computer tomography during treatment (right side).

Variants

- AFOP

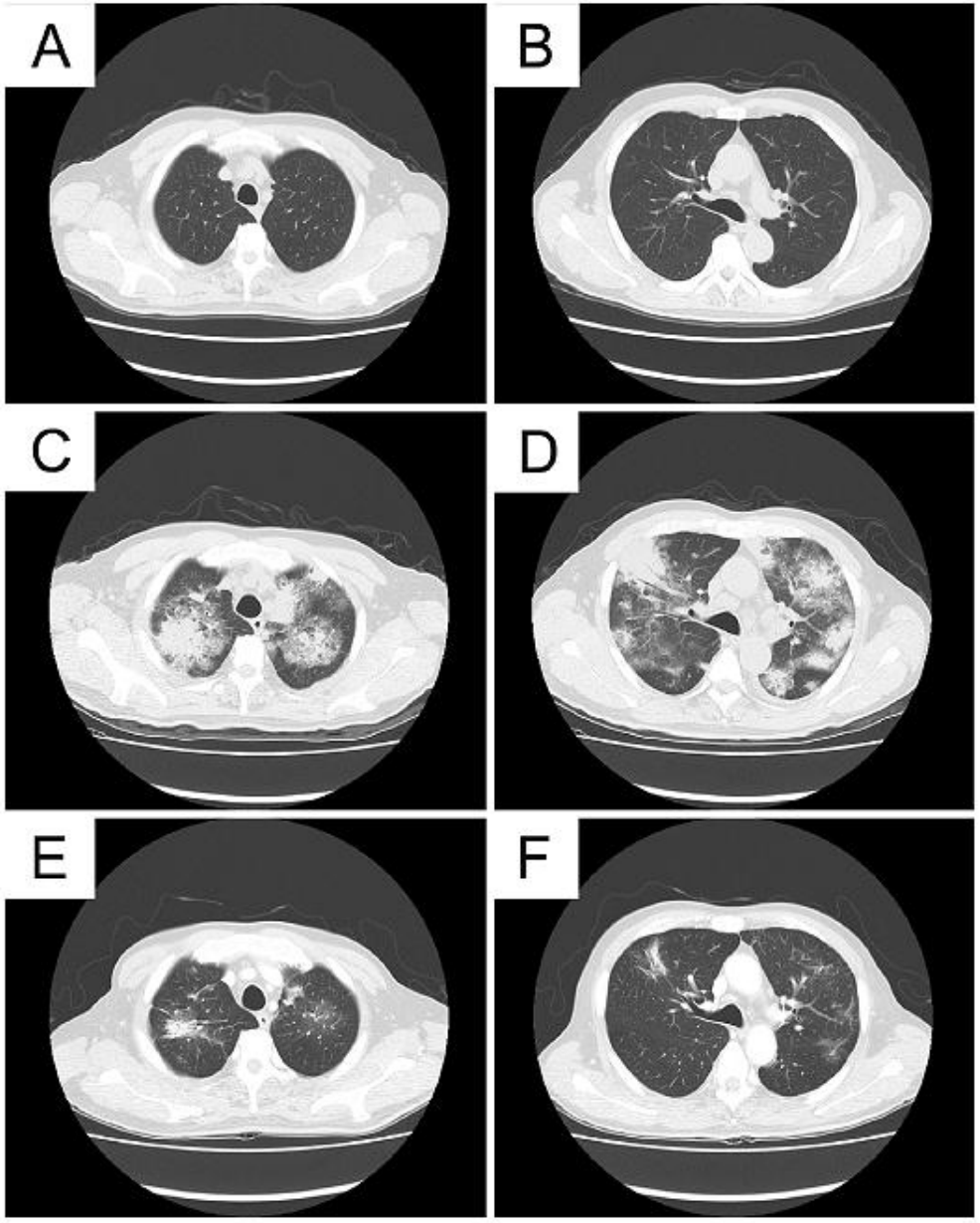
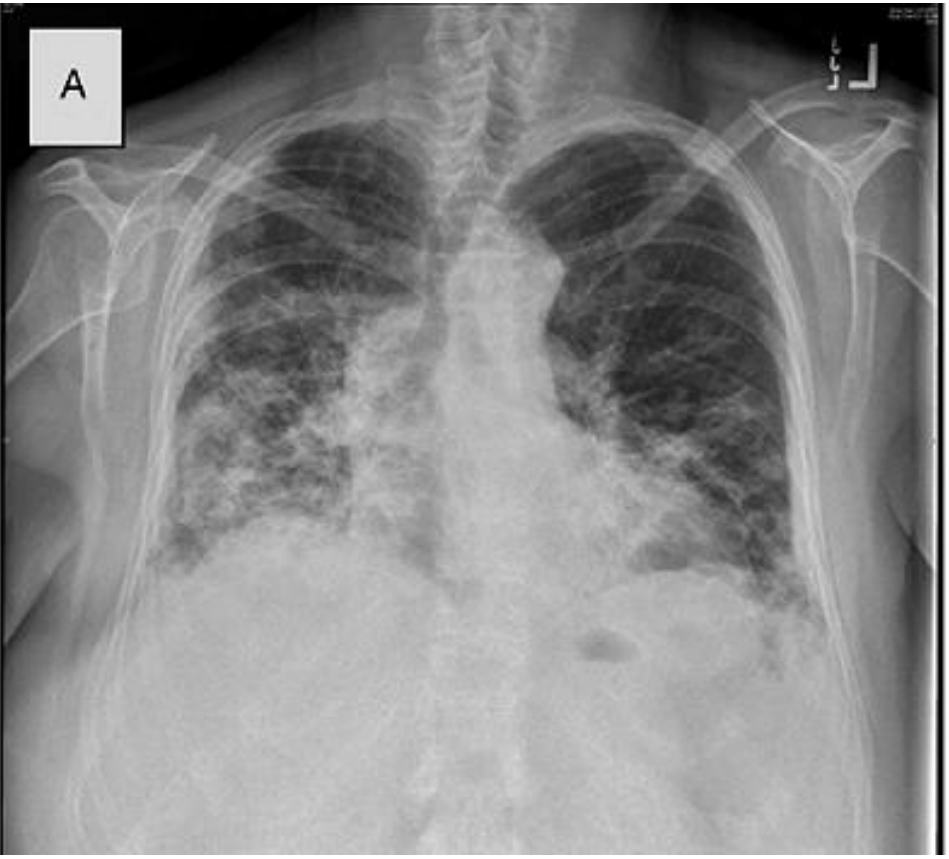
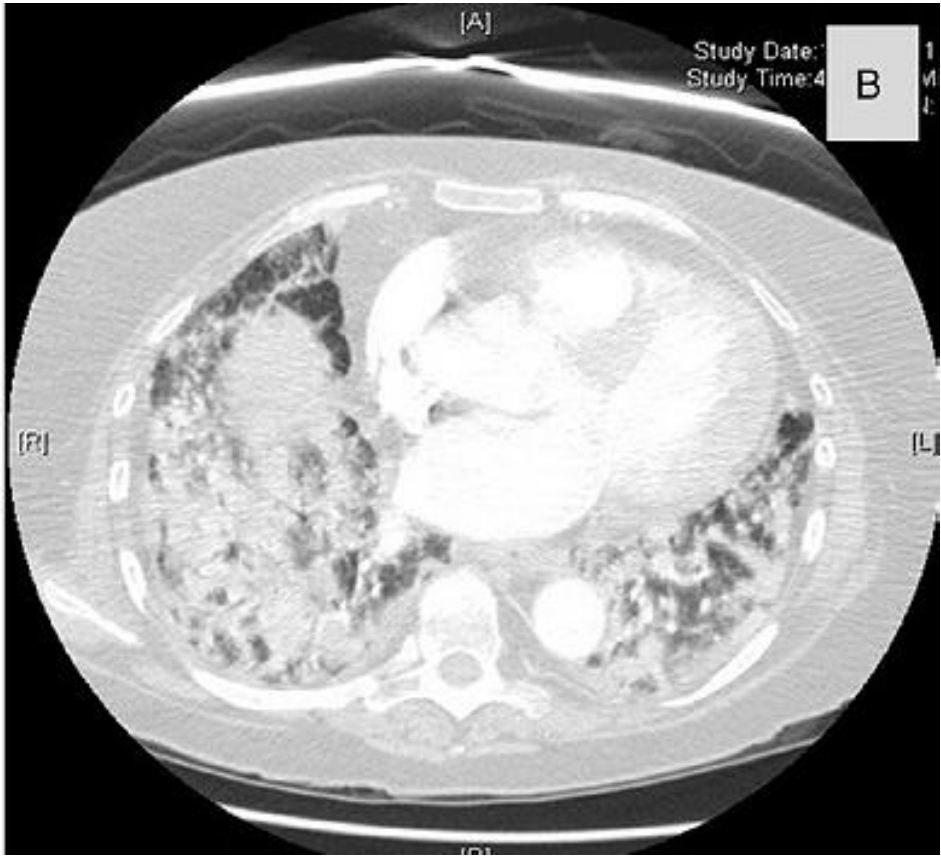


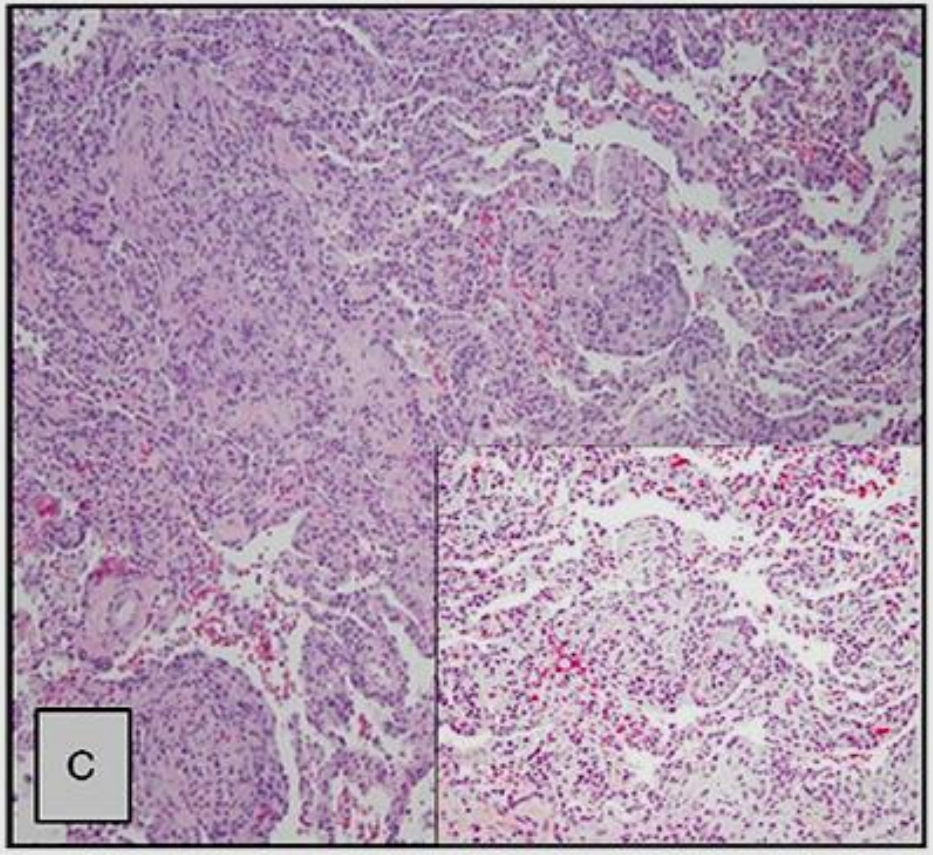
Figure 1. CT images. Chest CT images after treatment with nivolumab and at 15 weeks before the onset of dyspnea show normal findings (A, B). At the onset of ILD, multiple bilateral patchy infiltrates and ground glass attenuation with interlobular septal thickening developed (C, D). After treatment with corticosteroids, these findings all improved (E, F). ILD: interstitial lung disease

Barjaktarevic, 2013

- Ipilimumab in melanoma







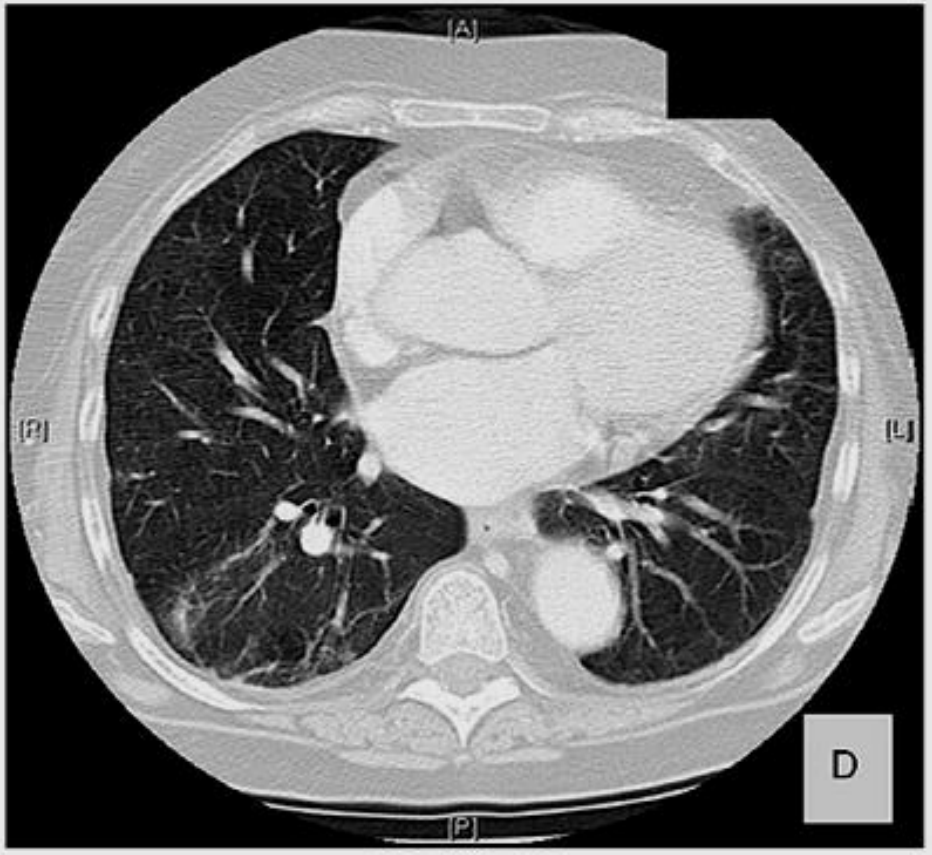
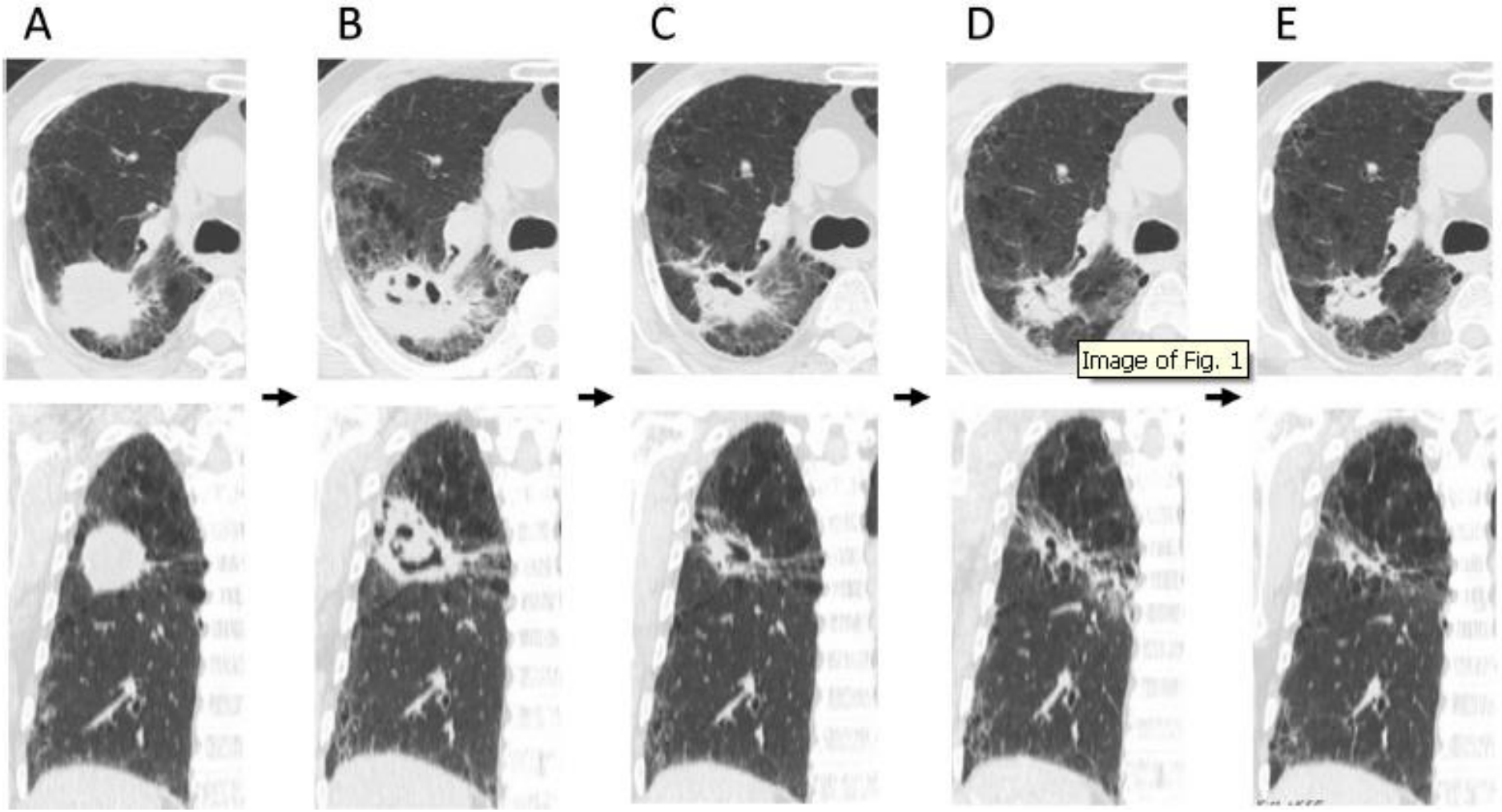


FIGURE 1. A, Chest radiograph on admission with bilateral patchy infiltrates, predominant in lower lung regions. B, Representative CT scan of chest 24 h after the admission showing extensive bilateral consolidation. C, Transbronchial biopsy specimen from right middle lobe showing intraalveolar granulation tissue with myofibroblasts and collagen consistent with organizing pneumonia; Masson bodies can be seen in the insert image (hematoxylin and eosin, original magnification × 100; inset, × 200). D, Repeat CT scan of chest 6 weeks after the admission with significant improvement of parenchymal changes.

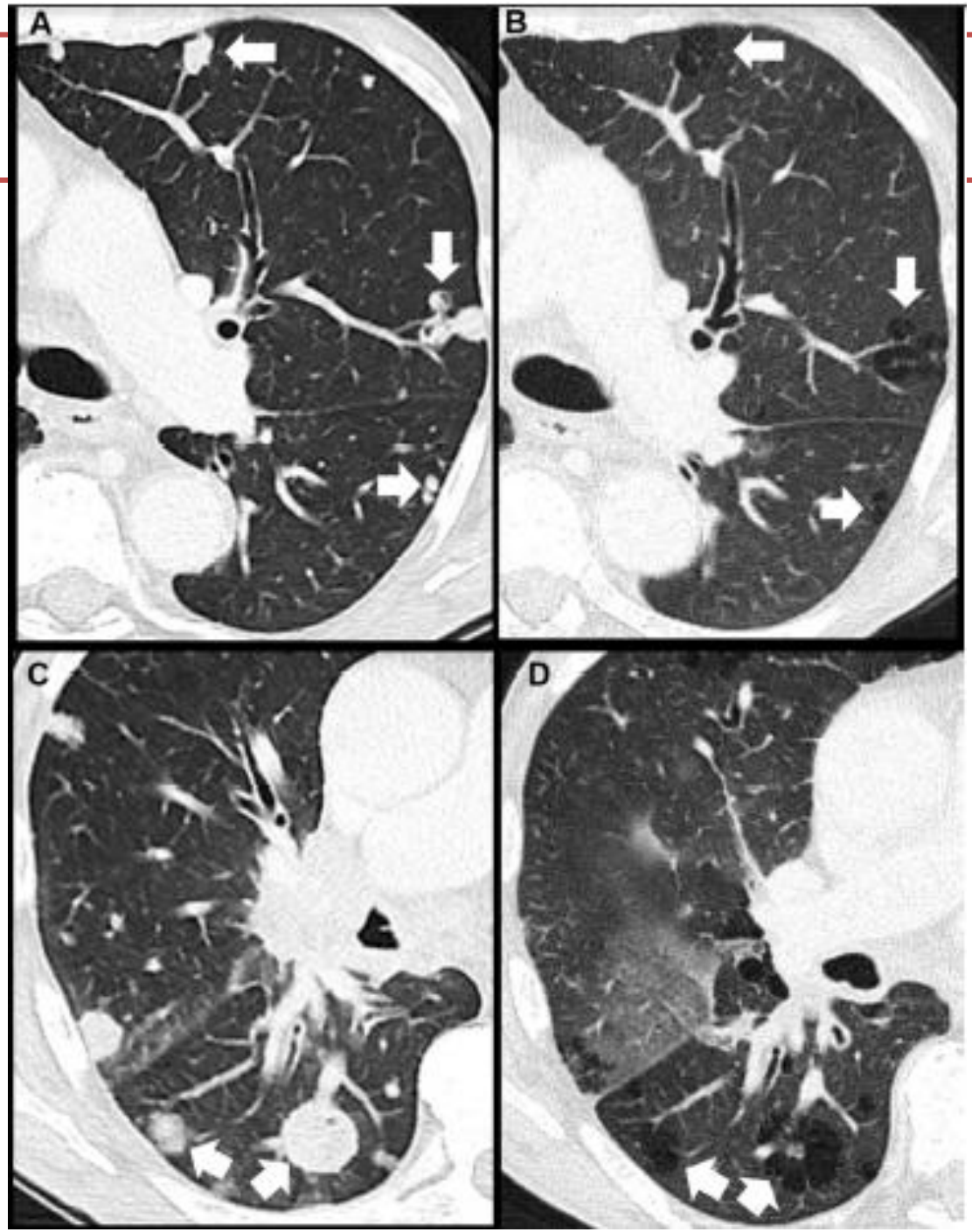
Tumoral cavitation

H. Kimura et al. / Lung Cancer 108 (2017) 7–8

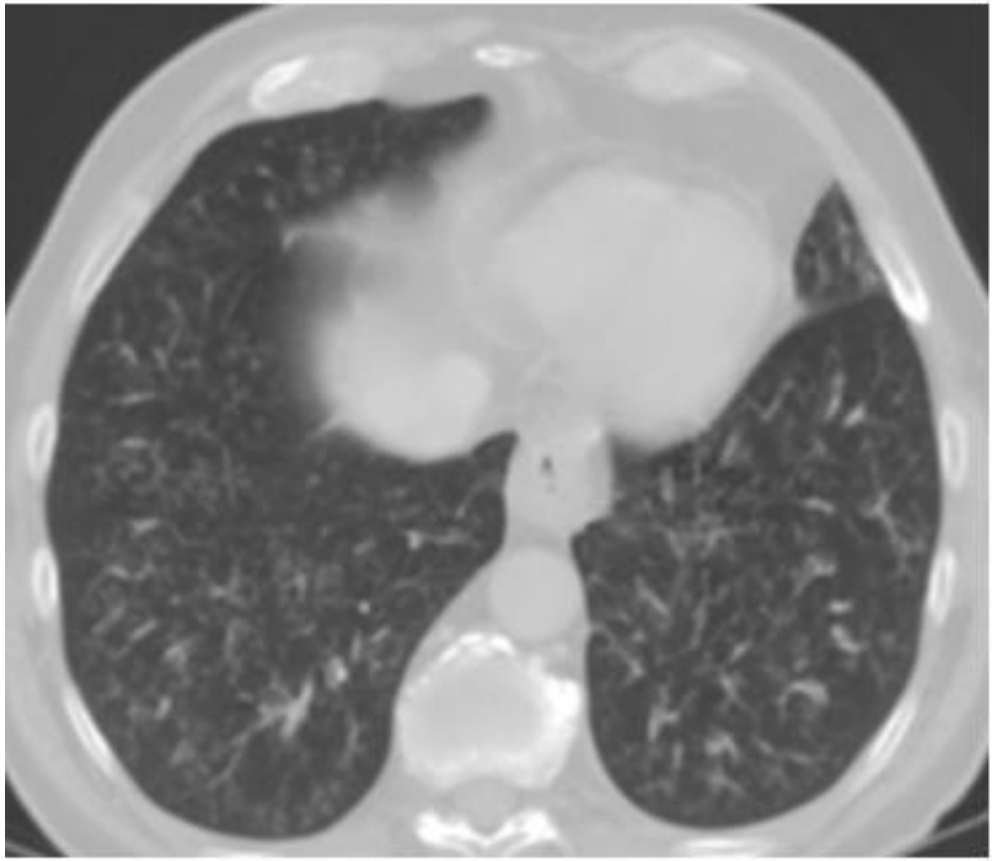


Cysts

- Rampinelli *et al*; 2017



- Tree-in-bud (consistent with subacute bronchiolitis)
- Some with CAO



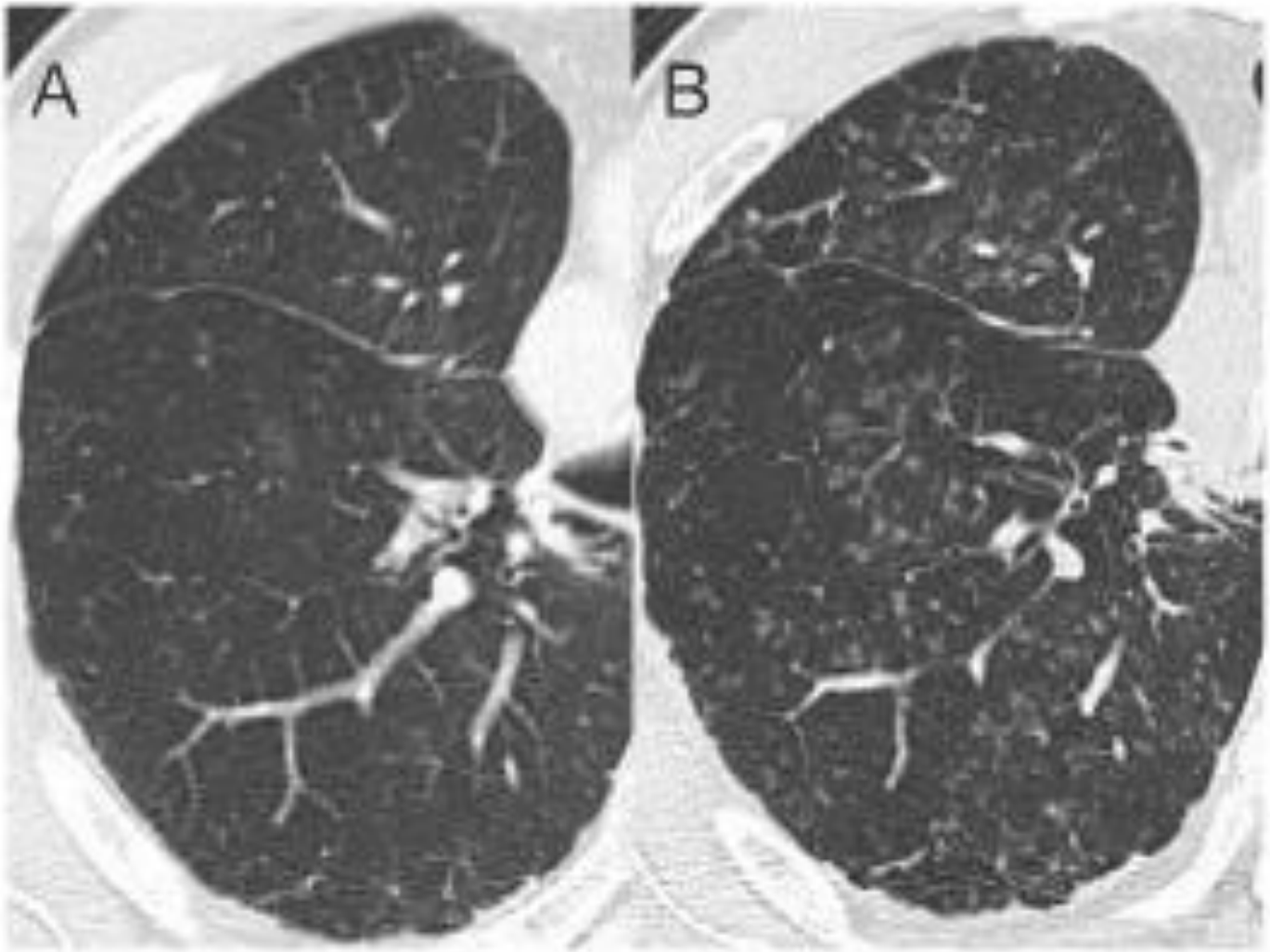


Fig. 1. Noncontrast chest computed tomography taken 5 months prior to admission (A) and on admission (B). Representative axial image demonstrate the diffuse nodular infiltration with inter- and intra-lobular septa or subpleural area.

Sarcoid-like granulomatous reactions

- Seen with ipilimumab, nivolumab, pembrolizumab
- 5-7% in melanoma patients exposed to ipilimumab or nivolumab
- 1,1-5,4 mo into Rx
- *De novo* or flare of previously diagnosed sarcoidosis
- In isolation or with bilateral upper or middle lung GGO, nodules or consolidation

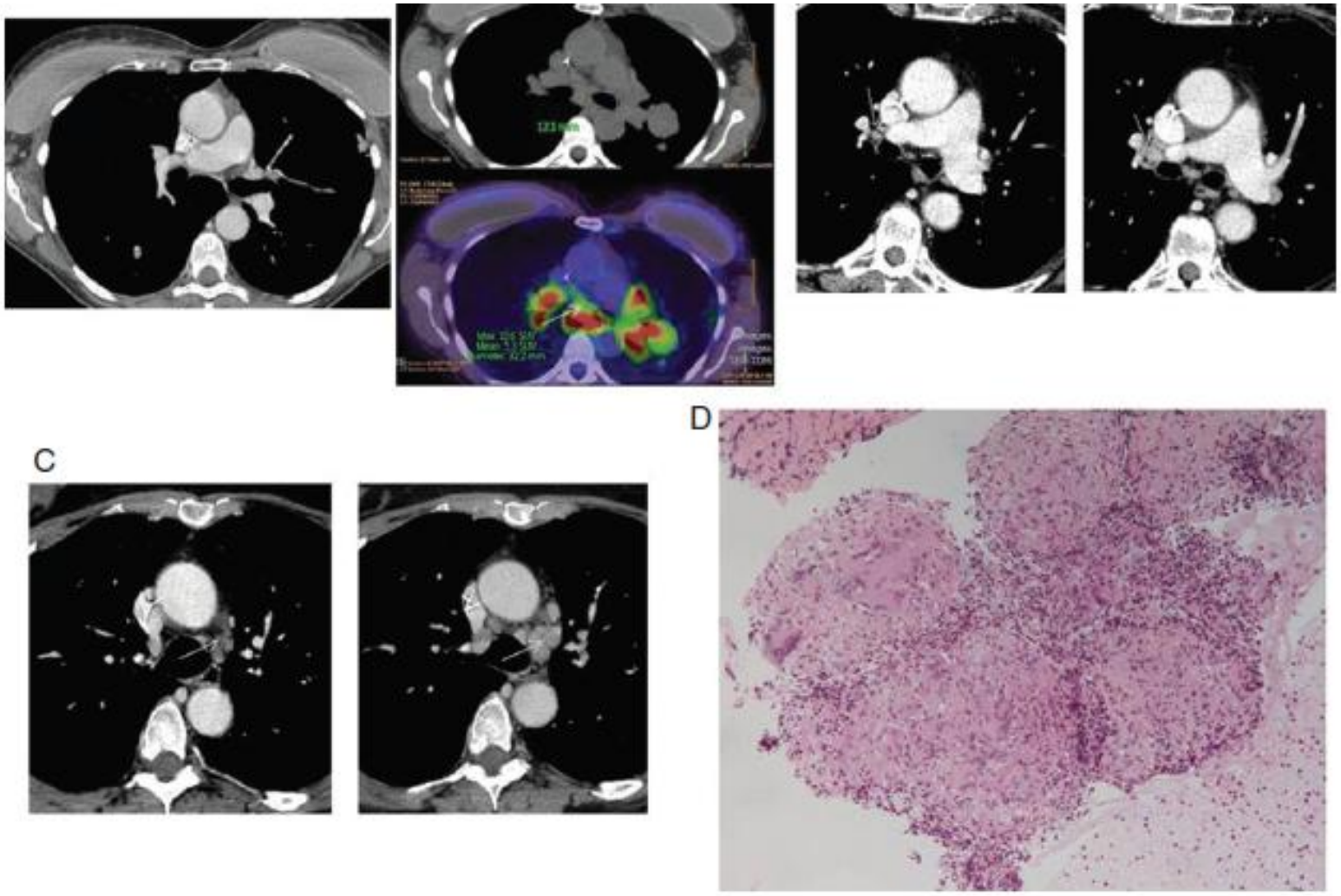
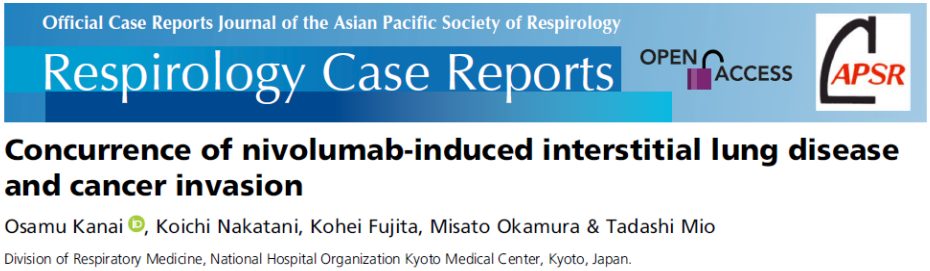


Figure 1. (A) CT scan and FDG–PET scan before and after 2 months of pembrolizumab treatment of the case report patient showing hypermetabolic mediastinal and hilar lymph nodes appearance. (B and C) CT scans of the second and third patients before and after 2 months of pembrolizumab treatment showing mediastinal lymph nodes appearance. (D) Lymph node biopsy showing well-formed giant cell granulomas.

Differential diagnosis



- Infection (pneumonia)
  - Pneumonia (*Chlamydia, Mycoplasma*, virus)
  - Opportunistic (if CST/Infliximab)
- DILD from drugs used to treat comorbidities
- Myocarditis - CHF - Pulmonary edema
- Particulars in lung cancer
  - Progression
  - Pseudoprogression - Tumoral inflammation
  - Atelectasis
  - Radiation-induced lung injury
  - Thromboembolism
  - Mixed patterns

Interfering IT-related conditions

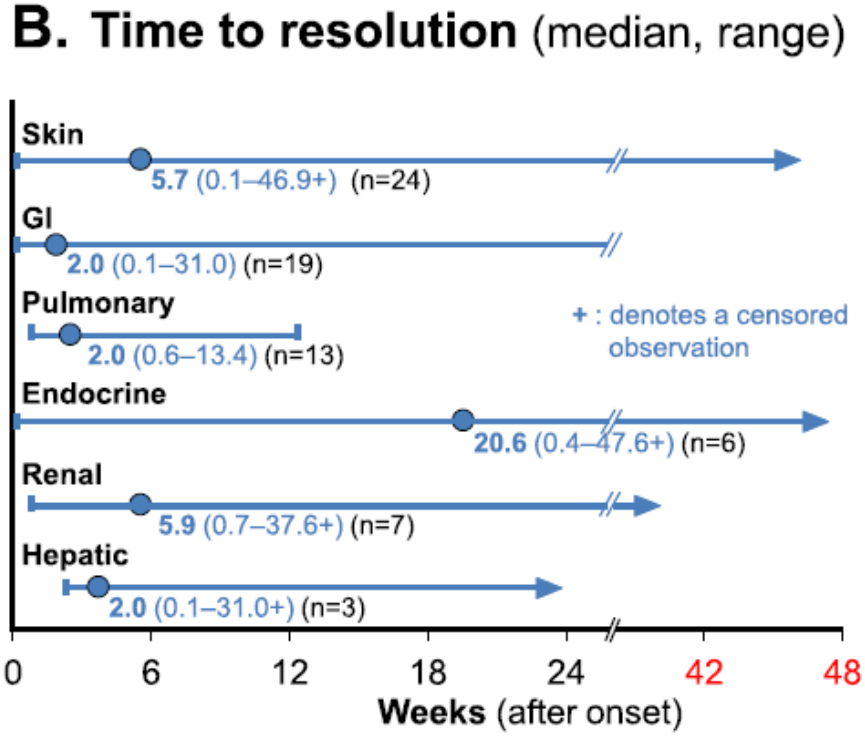
- 1-Thoracic nonpulmonary
  - Pericardial effusion w/wo tamponade
  - Cardiac involvement, myocarditis w/wo HF
  - Phrenic nerve injury
  - Myositis
- 2-Systemic - Distant
  - Myasthenia gravis
  - Thyroid storm
  - Adrenal failure

Outcomes in the real world

- 75%-85% improve
- Nishino, 2016
  - Corticosteroids: 17/20
  - Infliximab: 3
  - Restarted nivolumab therapy : 7
  - Relapse: 2 (were retreated with corticosteroids)
  - Pneumonitis flare after completion of corticosteroid taper : 1

Time to improvement with steroids

- Detectable response within 2-3 days
- Nivolumab: 3.3 weeks
- Combo ipilimumab + nivolumab: 6.1 weeks
- If steroids ≥20mg >1 month consider preemptive TMP



Rescue

- IVIG
- Infliximab
- Mycophenolate
- Tocilizumab

- Street drugs

Case Reports

"Smoking Wet"

Respiratory Failure Related to Smoking Tainted Marijuana Cigarettes

Christopher R. Gilbert, DO
Michael Baram, MD, FCCP
Nicholas C. Cavarocchi, MD, FACS

Reports have suggested that the use of a dangerously tainted form of marijuana, referred to in the vernacular as "wet" or "fry," has increased. Marijuana cigarettes are dipped into or laced with other substances, typically formaldehyde, phencyclidine, or both. Inhaling smoke from these cigarettes can cause lung injuries.

We report the cases of 2 young adults who presented at our hospital with respiratory failure soon after they had smoked "wet" marijuana cigarettes. In both patients, progressive hypoxemic respiratory failure necessitated rescue therapy with extracorporeal membrane oxygenation. After lengthy hospitalizations, both patients recovered with only mild pulmonary function abnormalities.

To our knowledge, this is the first 2-patient report of severe respiratory failure and rescue therapy with extracorporeal oxygenation after the smoking of marijuana cigarettes thus tainted. We believe that, in young adults with an unexplained presentation of severe respiratory failure, the possibility of exposure to tainted marijuana cigarettes should be considered. ***(Tex Heart Inst J 2013; 40(1):64-7)***

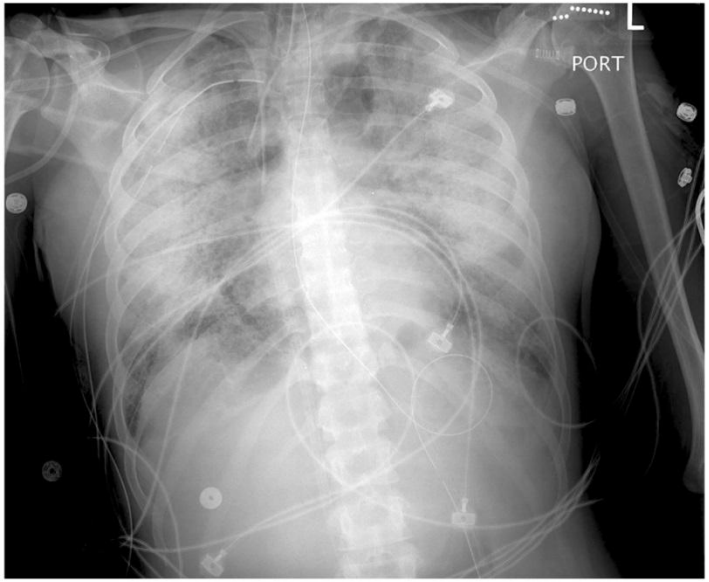


Fig. 1 *Patient 1. Chest radiograph at the time of ECMO cannulation shows diffuse pulmonary infiltrates bilaterally.*

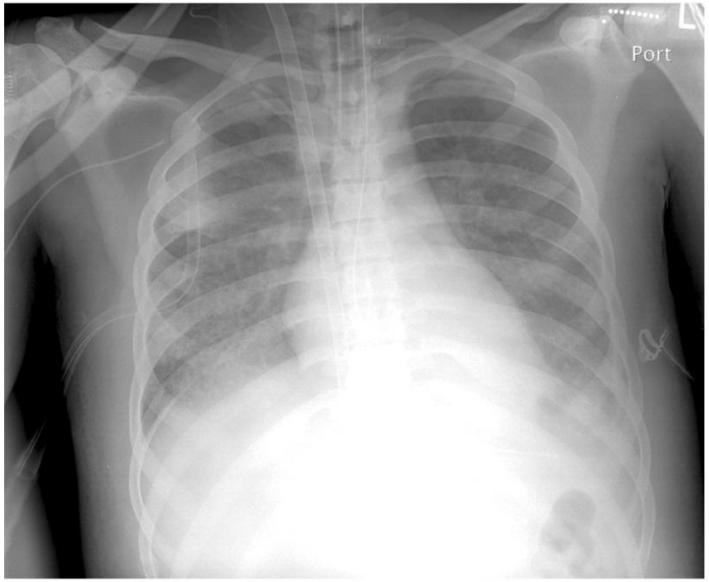
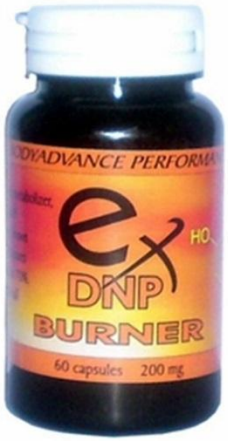


Fig. 2 *Patient 2. Chest radiograph at the time of ECMO cannulation shows diffuse pulmonary infiltrates bilaterally.*

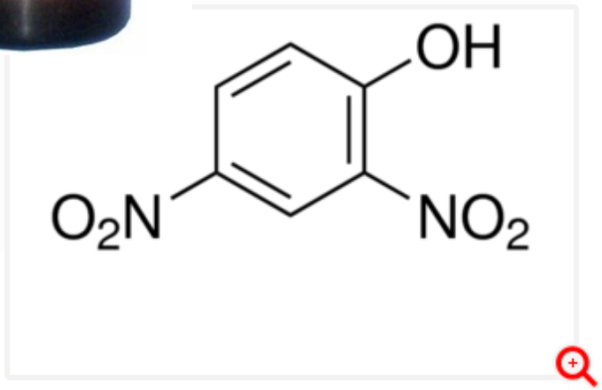


D198501 ALDRICH

2,4-Dinitrophenol

moistened with water, ≥98.0%

Synonym: α-Dinitrophenol, 2,4-DNP, DNP



FDS | SIMILAR PRODUCTS

CAS Number 51-28-5 | Linear Formula $(O_2N)_2C_6H_3OH$ | Molecular Weight 184.11 | Beilstein Registry Number 1246142

EC Number 200-087-7 | MDL number MFCD00007115 | PubChem Substance ID 24893583

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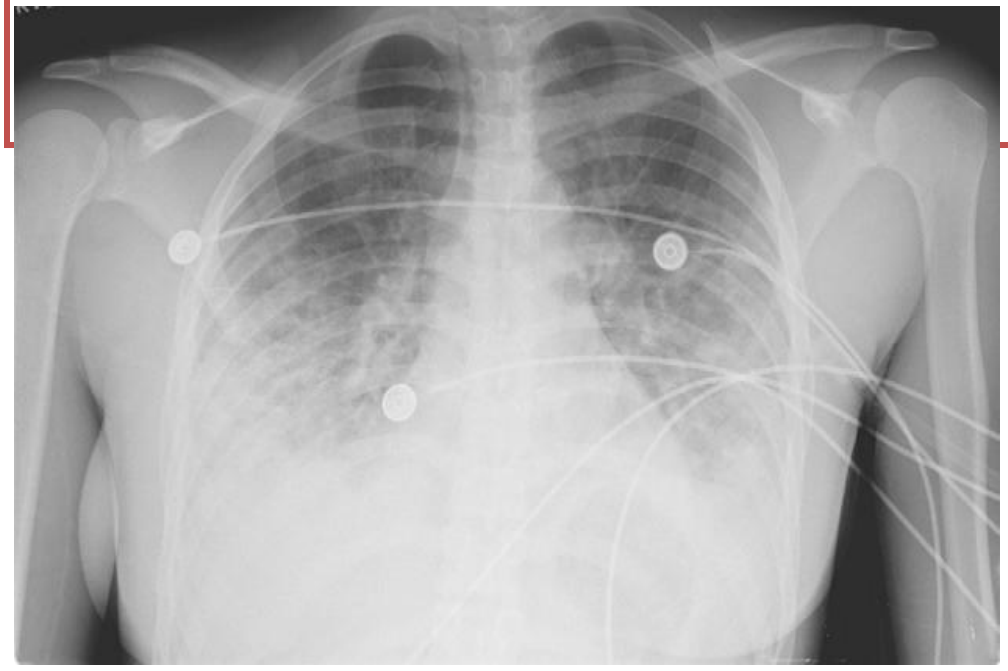
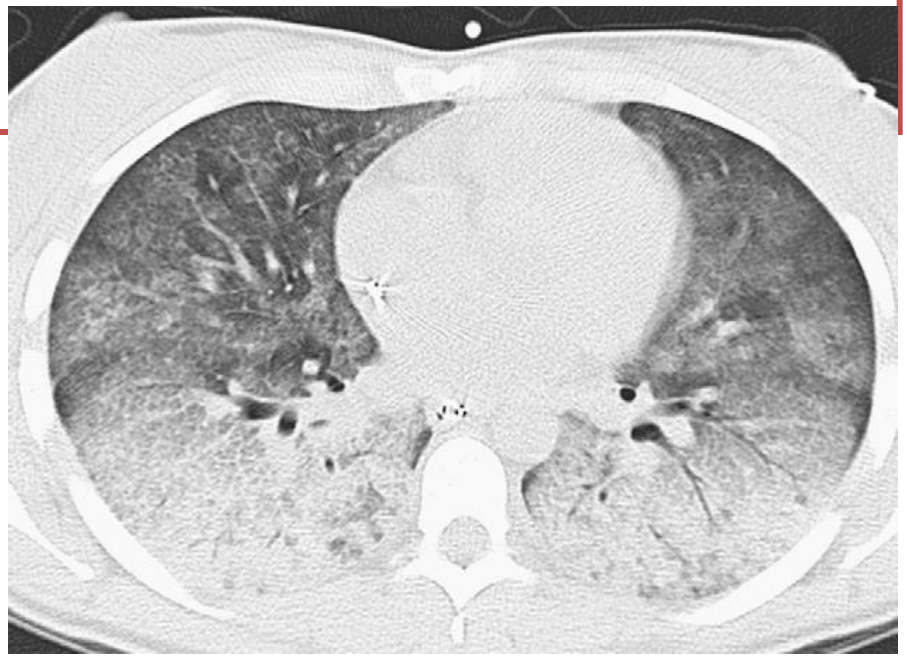
Propriétés

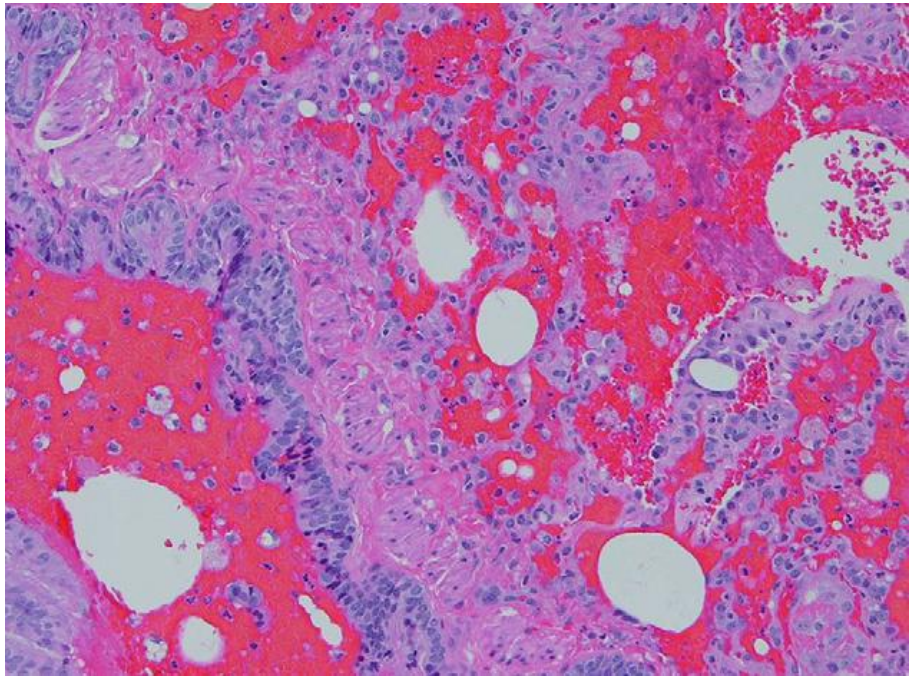
Related Categories	Building Blocks, C6 to C8, Chemical Synthesis, Organic Building Blocks, Oxygen Compounds, Plus...
vapor density	6.35 (vs air)
assay	≥98.0%
contains	≥15% water

Prix et disponibilité

Conditionnement - SKU	Disponibilité	Prix (EUR)	Quantité
D198501-5G	Disponible pour expédition le 23.09.15 - A PARTIR DE	26.60	0
D198501-100G	Disponible pour expédition le 13.10.15 - A PARTIR DE	31.20	0







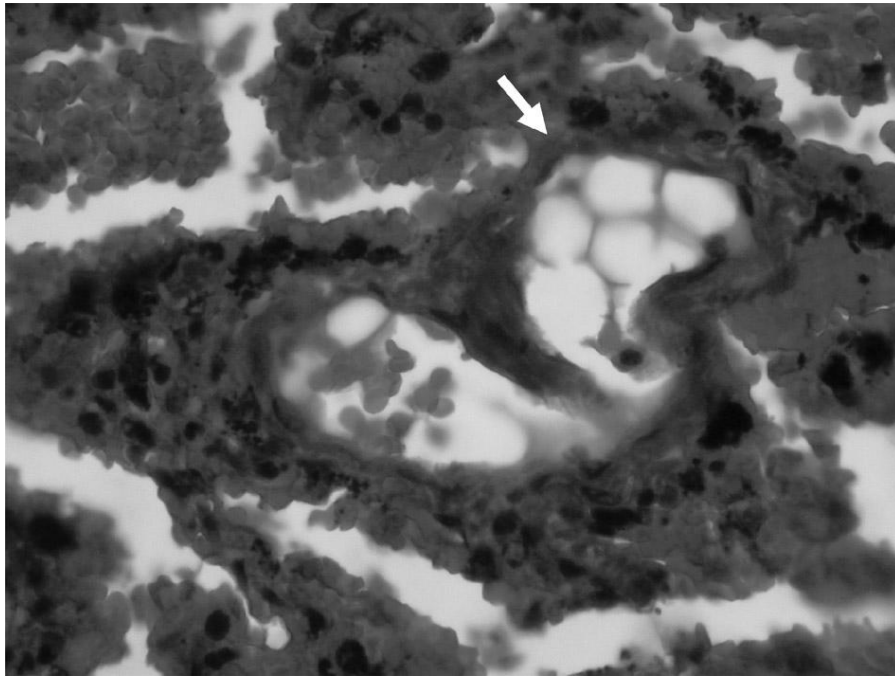
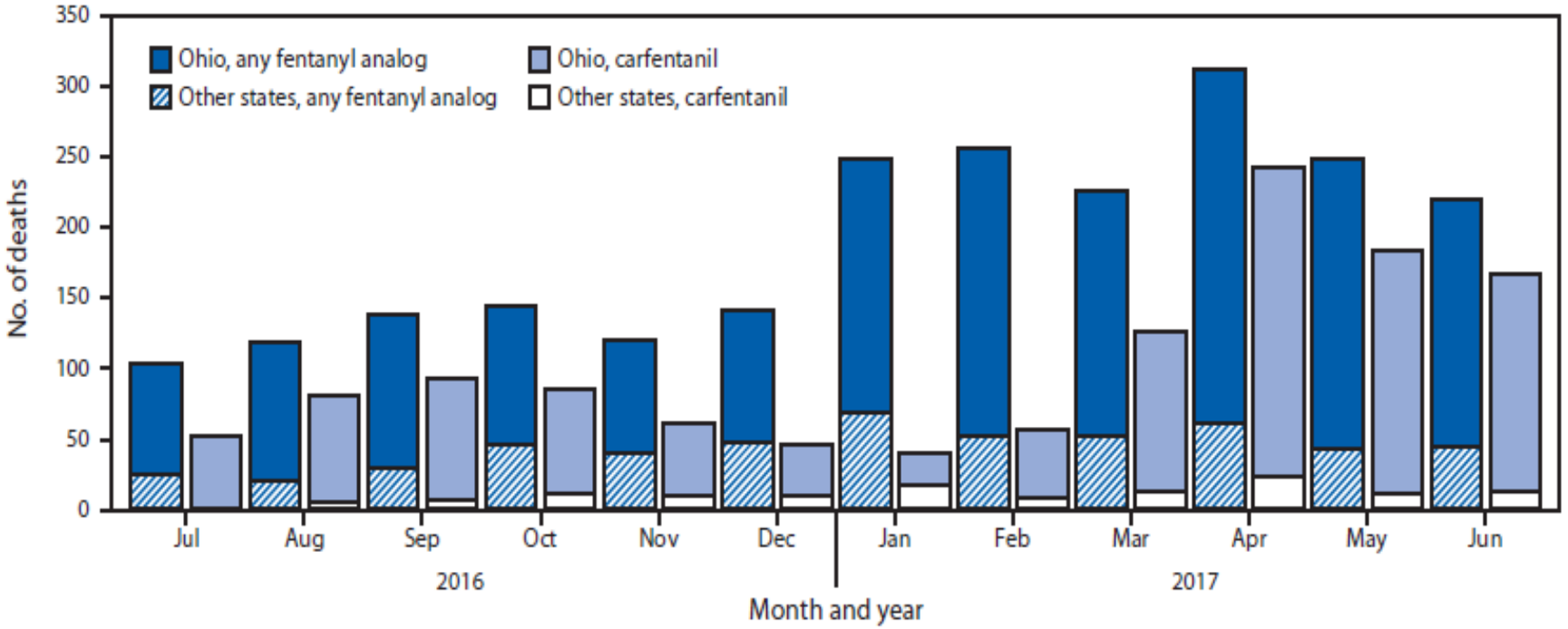


FIGURE. Number of overdose deaths with carfentanil and any fentanyl analog detected* — Ohio and nine other SUDORS states,† July 2016–June 2017



Drug 85 Times as Potent as Marijuana Caused a 'Zombielike' State in Brooklyn

By **MARC SANTORA** DEC. 14, 2016

Emergency workers treated a woman in Brooklyn in July in an area where people overdosed on a synthetic cannabinoid more potent than marijuana. Christopher Lee for The New York Times

RELATED COVERAGE


New York City Council Initiates Steps to Ban the Manufacture of K2 SEPT. 25, 2015


K2, a Potent Drug, Casts a Shadow Over an East Harlem Block SEPT. 2, 2015


33 Suspected of Overdosing on Synthetic Marijuana in Brooklyn JULY 12, 2016

- Fake fentanyl
- AMB-FUBINACA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

"Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York

Axel J. Adams, B.S., Samuel D. Banister, Ph.D., Lisandro Irizarry, M.D., Jordan Trecki, Ph.D., Michael Schwartz, M.D., M.P.H., and Roy Gerona, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Outbreak of Synthetic Cannabinoid–Associated Coagulopathy in Illinois

Amar H. Kelkar, M.D., Nichole A. Smith, M.D., Annia Martial, M.D., Harsha Moole, M.D., Michael D. Tarantino, M.D., and Jonathan C. Roberts, M.D.

ABSTRACT

BACKGROUND

In March and April 2018, more than 150 patients presented to hospitals in Illinois with coagulopathy and bleeding diathesis. Area physicians and public health organizations identified an association between coagulopathy and synthetic cannabinoid use. Preliminary tests of patient serum samples and drug samples revealed that brodifacoum, an anticoagulant, was the likely adulterant.

METHODS

We reviewed physician-reported data from patients admitted to Saint Francis Medical Center in Peoria, Illinois, between March 28 and April 21, 2018, and included in a case series adult patients who met the criteria used to diagnose synthetic cannabinoid–associated coagulopathy. A confirmatory anticoagulant poisoning panel was ordered at the discretion of the treating physician.

From the Departments of Medicine (A.H.K., N.A.S., A.M., H.M., M.D.T.) and Pediatrics (M.D.T., J.C.R.), University of Illinois College of Medicine at Peoria, and the Bleeding and Clotting Disorders Institute (M.D.T., J.C.R.) — both in Peoria. Address reprint requests to Dr. Kelkar at the Division of Hematology and Oncology, Department of Internal Medicine, University of Florida Shands Hospital, 1600 SW Archer Rd., Gainesville, FL 32610, or at amar.kelkar@medicine.ufl.edu.

N Engl J Med 2018;379:1216-23.
DOI: 10.1056/NEJMoa1807652

- Armstrong F, McCurdy M T, Heavner M S. Synthetic cannabinoid-associated multiple organ failure: Case series and literature review
  Pharmacotherapy 2019: *in press*

Adult Critical Care Medicine Attending Physician, University of Maryland Baltimore Washington Medical Center

Preface

Iatrogenic lung disease

Philippe Camus, MD

Edward C. Rosenow III, MD, MS

Guest Editors

Search results :

DIAGNOSING DIRD

Drugs 3	Patterns 1	Publications 11	Medias 0

Electronic cigarette, e-vaporizers/nicotine delivery systems (ENDS), vaping — 3

I.a I.b I.c I.d I.e I.j I.u I.v II.b III.a IV.d IV.n
IV.t VII.h VIII.d X.aq XI.r XI.ac XII.ag XV.c XV.p XV.x XV.y XVI.a
XVI.b XVII.a XIX.h XIX.n

Flavoring agents — 5

Nonsteroidal anti-inflammatory drugs (NSAIDs) — 5

I.c I.e II.a IV.a IV.f V.q VII.a VIII.a VIII.y IX.f X.a X.f
X.g

I - Interstitial/parenchymal lung disease

Ia	Pneumonitis (ILD), acute, severe (may occasion an ARDS picture)	1
Ib	Pneumonitis (ILD)	1
Ic	Eosinophilic pneumonia (pulmonary infiltrates and eosinophilia)	1
Id	Organizing pneumonia pattern (an area or areas of consolidation on imaging)	1
Ie	Acute eosinophilic pneumonia (AEP)	1
If	Lipoid pneumonia, exogenous	1
Iu	Relapsing or migrating pneumonitis/pneumonia (see also Id)	1
Iv	Altered lung function/PFTs (can be subclinical)	1

II - Pulmonary edema - Acute lung injury - ARDS

IIb	ARDS - Acute lung injury	1

III - Pulmonary/alveolar hemorrhage

IIIa	Alveolar hemorrhage, diffuse (DAH)	1

IV - Airway involvement

IVd	Cough (lone)	2
IVn	Obstructive airway dysfunction (see also IVc)	1
IVt	Bronchitis, chronic bronchitis, bronchorrhea	1

VII - Mediastinal involvement

VIIh	Pneumomediastinum	1

FREQUENCY OF DRUG REPORTS