Drug-induced ILD: Epidemiology-classification

- **Department of Pulmonary & Intensive Care**
  Université de Bourgogne
  Dijon - France

- Laughlen G.F.
  Studies on pneumonia following naso-pharyngeal injections of oil
  Am J Pathol, 1925. 1: 407-414
- Omarini, C. et al.
  Pneumonitis and pulmonary fibrosis associated with breast cancer treatments
  Breast Cancer Res Treat, 2014

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

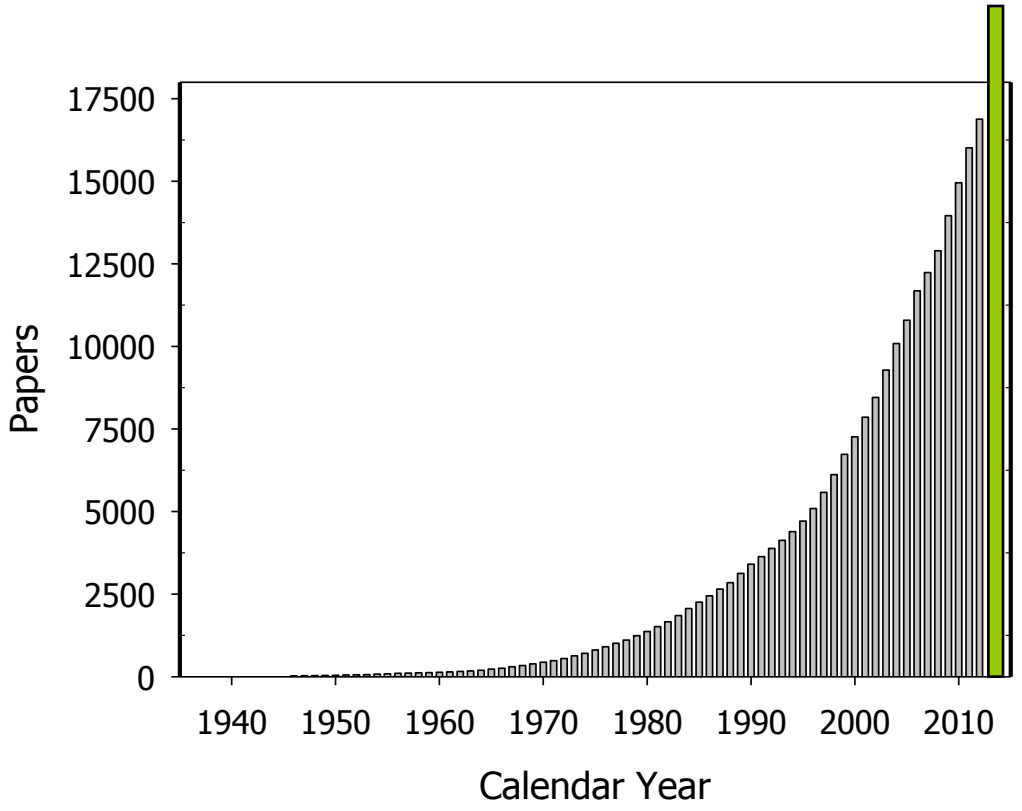
Drug-Induced Lung Disease: The Price of Progress

- ***Ca.* 120 drugs**

Drug-induced and iatrogencic lung disease

- Therapy drugs
- Drugs of abuse (heroin, cocaine, meth-, MDMA)
- Blood & blood products
- Chemicals (paraquat, superwarfarins)
- Excipients (peanut-, castor oil, talc, crospovidone)
- Adulterants, curring agents: levamisole, warfarin
- Acrylate cement, hyaluronate, Hydrogel
- Gasses: O2, NO
- Irradiation
- Herbal therapy

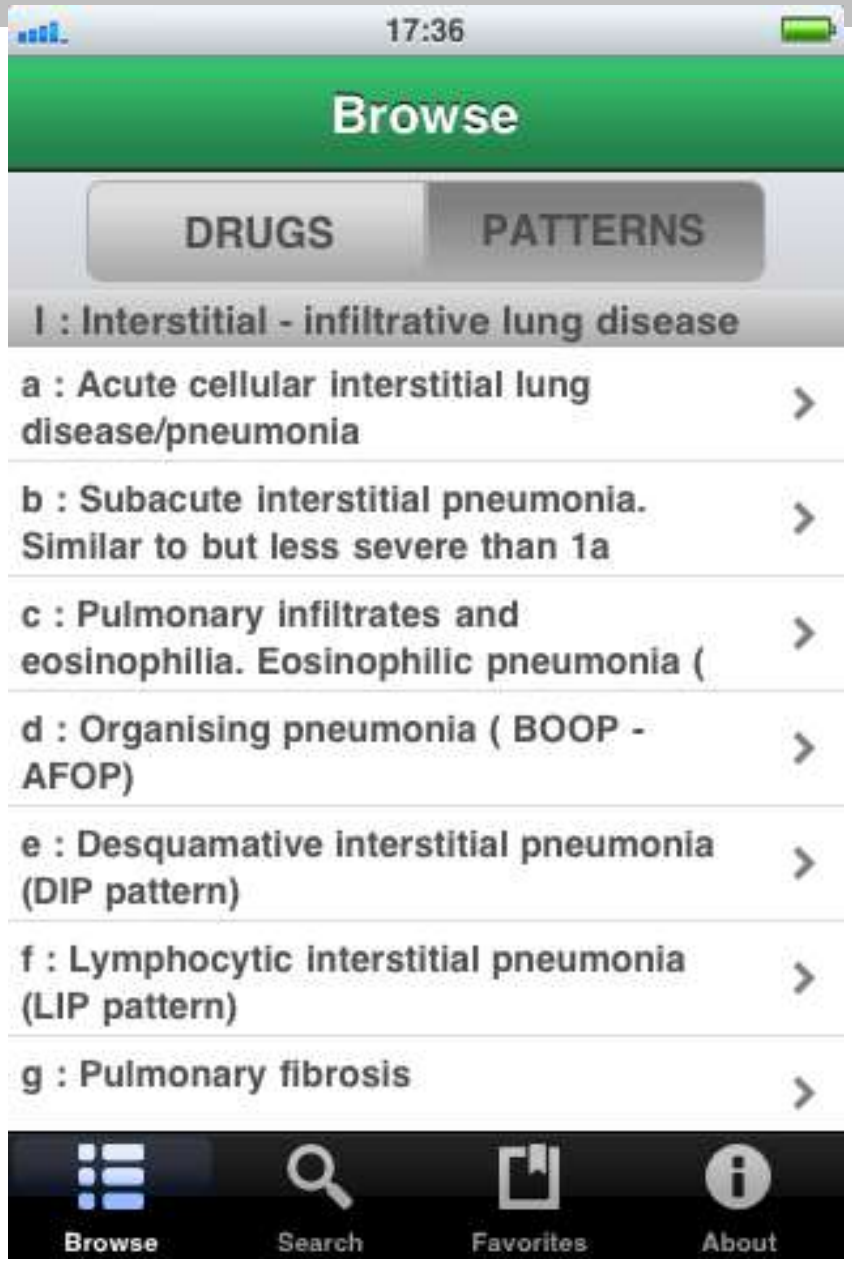
- **Literature**
  - **20.500 references**
  - **~9.000.pdf**
  - **1500 new papers/year**



894 drugs/procedures

- **20 main patterns**
- **220 sub patterns**
- **33 ILD patterns**


17:36
Browse
DRUGS
PATTERNS
A
Abacavir
1
Abciximab
4
Acebutolob
2
Acetaminophen
0
Acetazolamide
4
Acetylcysteine
5
Acetylsalicylic acid
5
Browse
Search
Favorites
About


17:36
Browse
DRUGS
PATTERNS
I : Interstitial - infiltrative lung disease
a : Acute cellular interstitial lung disease/pneumonia
b : Subacute interstitial pneumonia. Similar to but less severe than 1a
c : Pulmonary infiltrates and eosinophilia. Eosinophilic pneumonia (
d : Organising pneumonia (BOOP - AFOP)
e : Desquamative interstitial pneumonia (DIP pattern)
f : Lymphocytic interstitial pneumonia (LIP pattern)
g : Pulmonary fibrosis
Browse
Search
Favorites
About

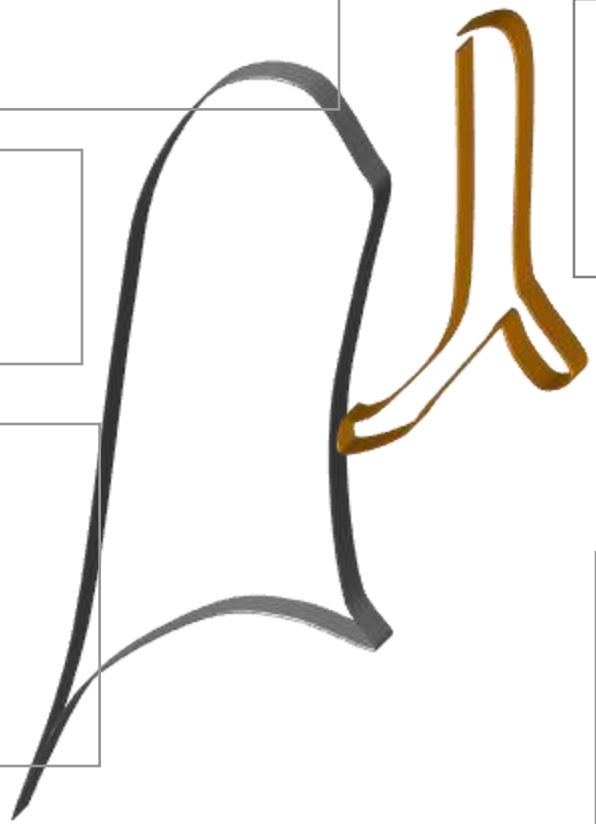
Classification

Lung parenchyma ~75%
NSIP (cellular/fibrotic)
DAD
Pulmonary edema
DAH
Opportunistic infection

Central airway
Angioedema
Hematoma

Lower airways
Cough
Acute bronchospasm
Obliterative bronchiolitis

Vasculopathy
PHT
Thromboembolism



Mediastinum
Lymphadenopathy
Lipomatosis

Pleura
Effusion
Thickening
Chest pain
Pneumothorax

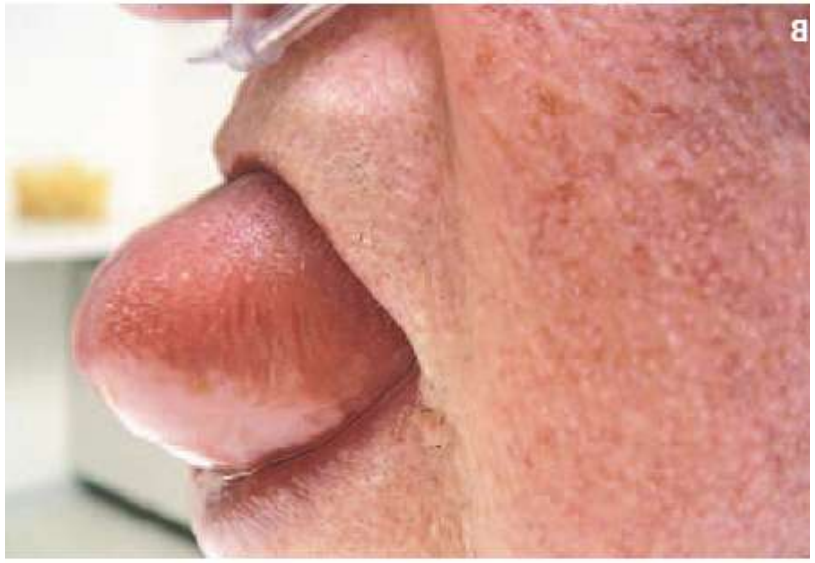
Heart
Pericardial effusion
Myocarditis
Valvular heart disease

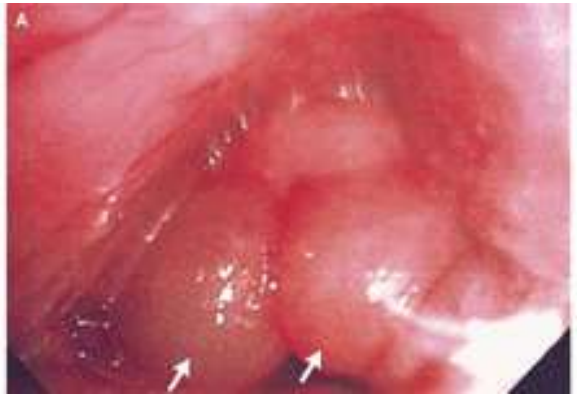
Hemoglobin
Methemoglobinemia

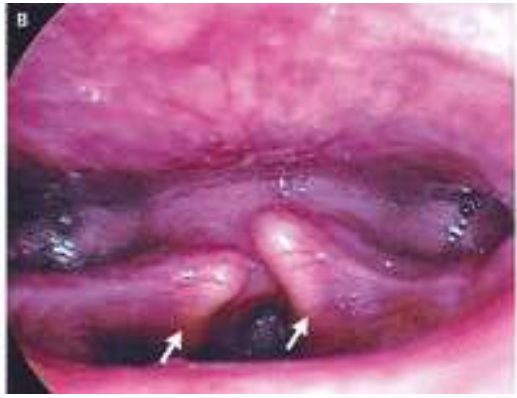
Neuromuscular
Acute respiratory failure

Upper airway angioedema

- Isolated UAO: ACE inhibitors
- UAO & anaphylaxis: antibiotics, NSAIDs, chemo agents, biologicals
- Maintain airway patency
- Icatibant - Epinephrine







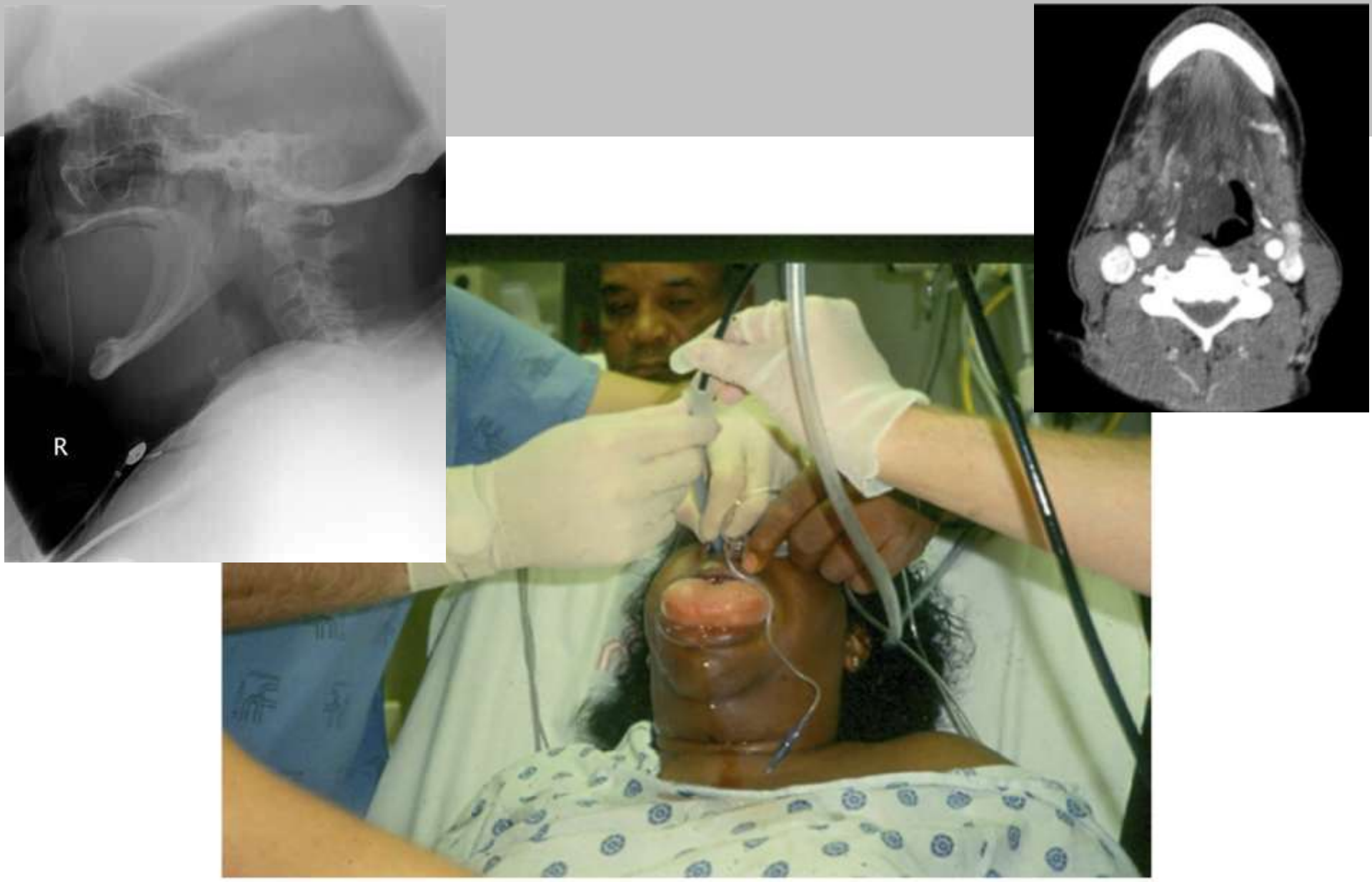


Figure 1. Example of life-threatening ACE inhibitor–induced angioedema with attempted emergency fiber optic nasotrachael intubation. The procedure was unsuccessful, and an emergency cricothyroidotomy was performed with great difficulty.

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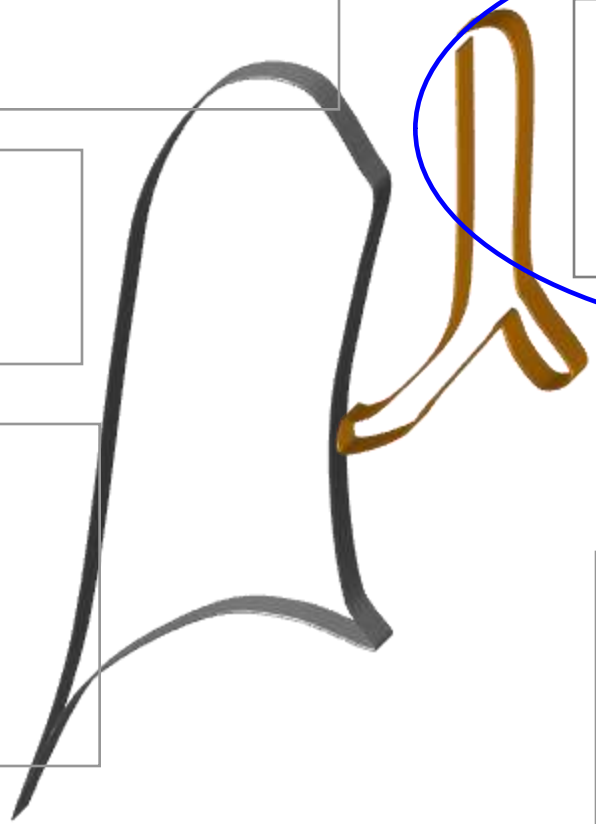

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Neuromuscular
Acute respiratory failure

Catastrophic bronchospasm - AAA

- **Causal drugs**
  - **Nonselective ß-blockers: propranolol**
  - **NSAIDs - ASA**
  - **Abused substances**
    - Heroin
    - Cocaine
    - Alcohol
- **Dry cinnamon challenge**

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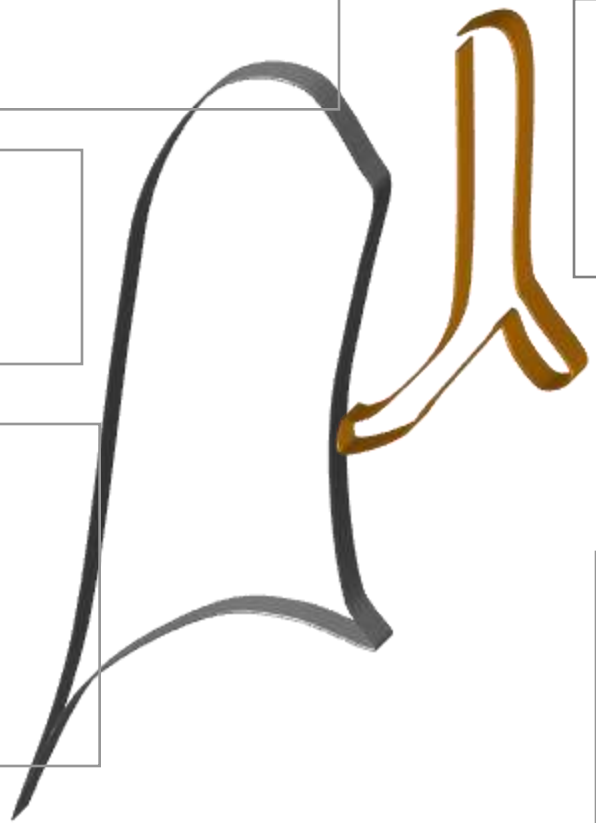

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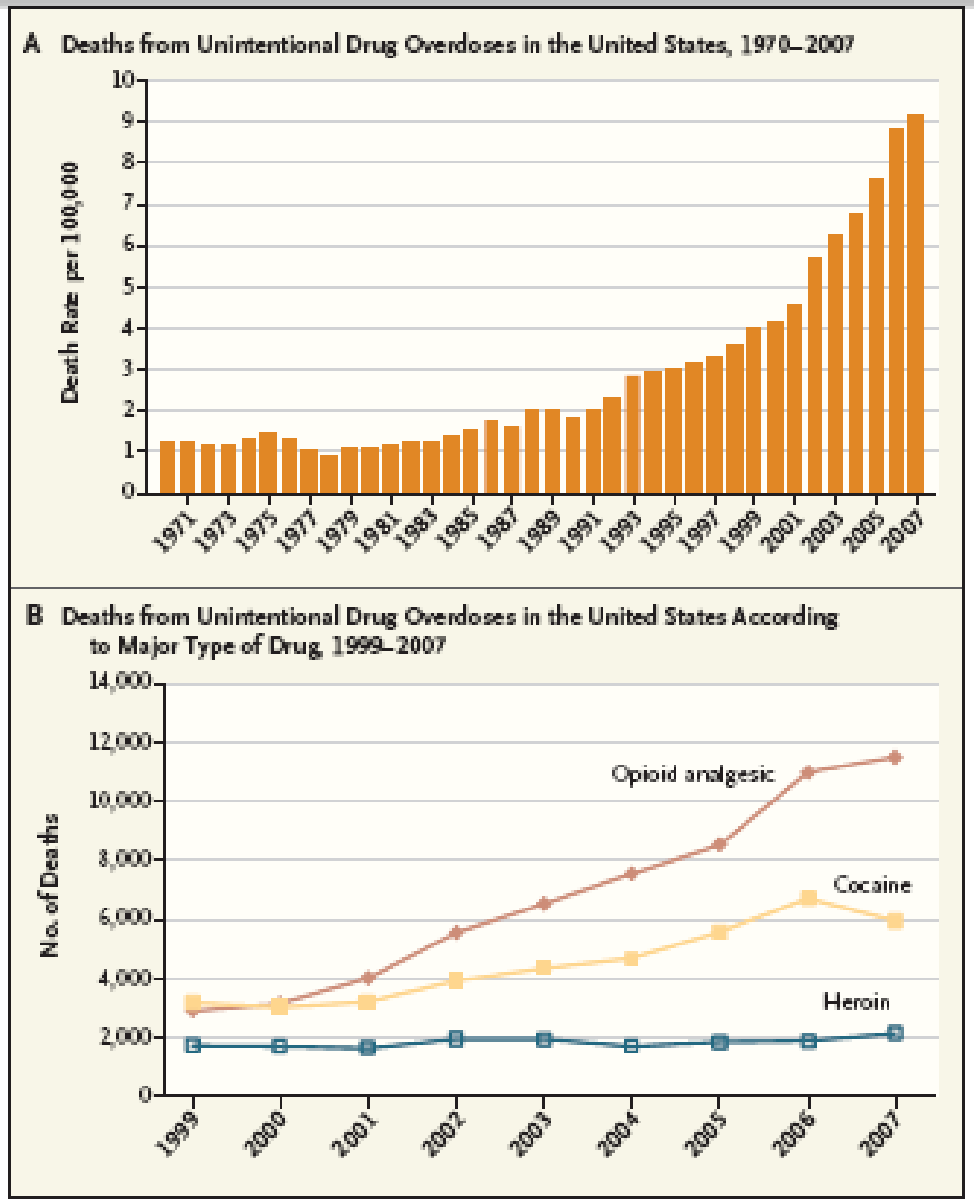

U.S. Rates of Death from Unintentional Drug Overdoses and Numbers of Deaths, According to Major Type of Drug.

Shown are nationwide rates of death from unintentional drug overdoses from 1970 through 2007 (Panel A) and the numbers of such deaths from opioid analgesics, cocaine, and heroin from 1999 through 2007 (Panel B). Data are from the National Vital Statistics System, Centers for Disease Control and Prevention.

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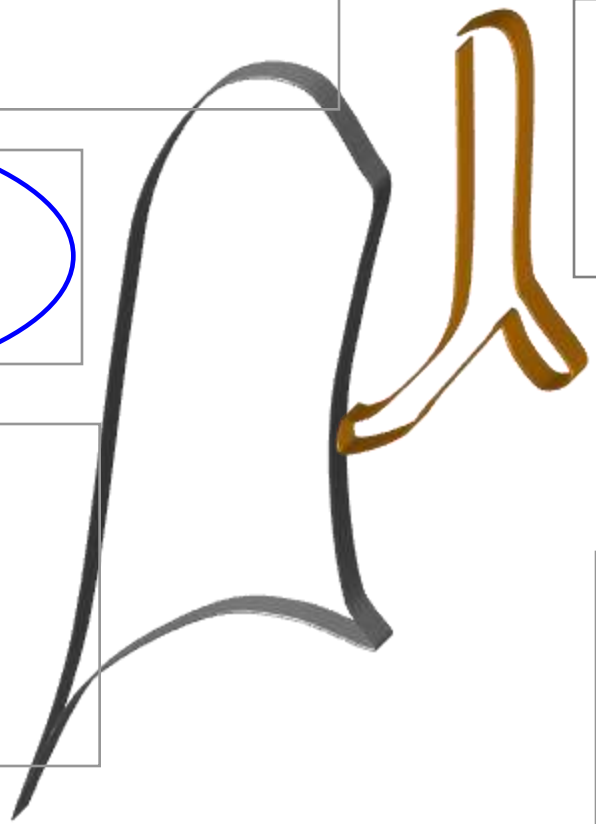

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Pulmonary vasculopathy

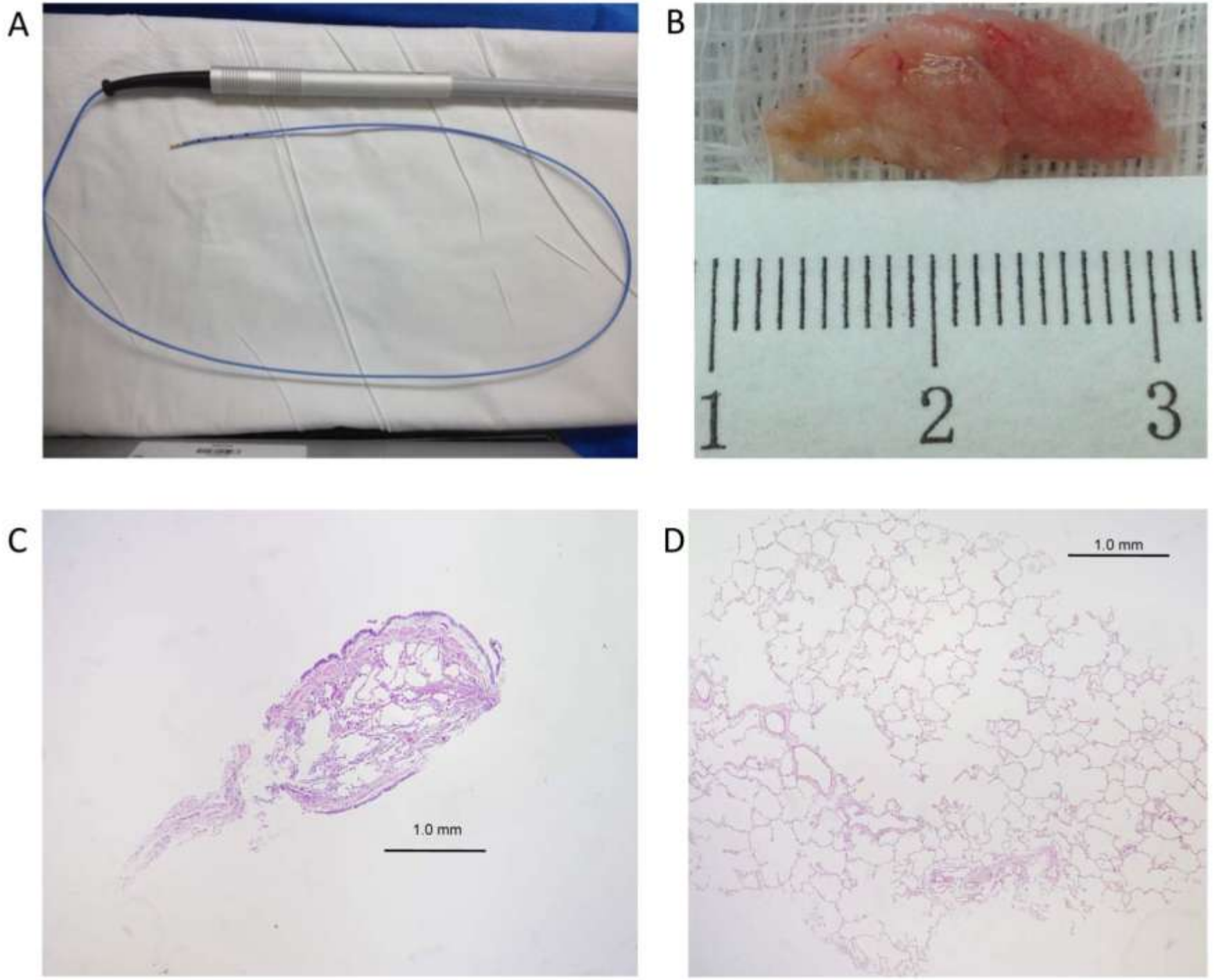
- **Pulmonary hypertension**
  - **Anorexigens**
    - Aminorex, fenfluramine, benfluorex
    - Recreational aminorex
    - Aminorex from levamisole
  - **Dasatinib**
  - **Interferons**
  - **Abused amphetamines**
  - **Crushed tablets**
- **PVOD**
  - **Mitomycin C**

DI Interstitial lung disease

- 28% of publications
- *Ca.* 75% of DI cases
- Drugs may 'produce' virtually any known ILD pattern
- Drug withdrawal leads to improvement in a sizable fraction

Pathology

- *'Regarding drug-related injury, no histopathologic changes are specific for any drug, despite any claims in the literature to the contrary'*
  Leslie K Arch Pathol Lab Med, 2007; 131: 407
- **TBLB 'unreliable'**
- **OLB: 4.5-6.9%**
- **VATS: Mortality up to 2.1%**


A
B
1
2
3
C
1.0 mm
D
1.0 mm

Caution when relating imaging and pathology

- **Cleverley 2002: 20 ILD**
  - Concordant: 45%
  - Discordant: 55%
- **Blackhall 2013: 103 ILD**
  - Concordant: 18.4%
  - Discordant: 51.5%
  - No diagnosis: 30.1%
- **Kayatta 2013: 194 ILD**
  - Concordant: 15%

EPIDEMIOLOGY

ILD fraction attributable to drugs/radiation

- **Netherlands: Thomeer 2001**

Table 1.—Comparison of distribution of interstitial lung diseases in different registries

	Flanders*		Germany#	Italy		New Mexico§	
	Prevalent	Incident	Incident	Prevalent¶	Prevalent+	Prevalent	Incident
Total number	362	264	234	4169	1138	257	202
Sarcoidosis	112 (31)	69 (26)	83 (35)	2199 (53)	344 (30)	30 (12)	16 (7.8)
IPF (UIP, DIP, LIP)	62 (17)	50 (19)	76 (32)	805 (19)	417 (37)	58 (23)	63 (31)
BOOP	10 (2.3)	9 (3.4)	16 (6.8)	26 (0.6)	57 (5)	0	1 (0.5)
(C)EP	9 (2.5)	7 (2.7)	0	42 (1.0)	27 (2.3)	3 (1.2)	1 (0.5)
Connective tissue disease	27 (7.5)	19 (7.2)	5 (2.1)	125 (3.0)		33 (13)	18 (8.9)
Goodpasture, Wegener, Churg Strauss	5 (1.4)	4 (1.5)	2 (0.8)	62 (1.5)	25 (2.2)	2 (0.8)	7 (3.5)
Hypersensitivity pneumonitis	47 (13)	32 (12)	25 (11)	162 (3.9)	50 (4.3)	0	3 (1.5)
Drug/radiation‡	12 (3.3)	12 (5)	6 (2.6)	87 (2.1)	21 (1.8)	6 (1.9)	7 (3.5)
Eosinophil granuloma/histiocytosis X	13 (3.6)	7 (2.7)	0	34 (0.8)	73 (7.2)	2 (0.8)	0
Pneumoconiosis**	19 (5.0)	18 (6.8)	6 (2.6)	417 (10)		36 (14)	21 (10)
Fibrosis (postinflation, not defined)	33 (9.1)	27 (10)	12 (5.1)			83 (32)	61 (30)
Others	13 (3.6)	10 (3.8)	0	210 (5.0)	124 (11)	5 (1.9)	4 (1.9)

- **Denmark: Hylgaard 2014: 5%**
- **India/Turkey: Yoh 2010: 1.08%; Musellim: 1.7%**

- **Nonchemo drugs**
  - Amiodarone: 3.8% *vs.* 1.5% in CTR (1.43% p-y)
  - Leflunomide: 1.2% (8.1/10,000 p-y)
  - Lenalidomide: 3.4%
  - Methotrexate: 0.43-9%
  - Nitrofurantoin: 0.02% (acute/chronic 1/5)
  - I-mTOR (sirolimus, everolimus): 6-36%

  - In SOT recipients: ~3%

Chemotherapy drugs

- **BCNU: 2%**
  - intensive: 19.3% (44% mortality)
- **CCNU: 1%**
- **ATRA: 7.8%**
- **Bleomycin 1-11% (Fatal in 10-60%)**
  - + radiation: 42%
- **Busulfan high dose: 3.6%**
- **Docetaxel 2-4.6% (25.9% if preexisting ILD)**
- **Erlotinib: 0.4%**
- **Fludarabine: 8.6%**
- **Gefitinib: 3.2-4.5% (1% in the west)**
- **Gemcitabine: 0.2%**
- **Paclitaxel: 3%**

Drug regimens +/- radiation (average: 1-6%)

- Cyclophosphamide+methotrexate+etoposide: 24%
- Gemcitabine + blemoycin: 22%
- Gemcitabine/Pemetrexed + platinum: 5.8%
- Weekly gemcitabine + docetaxel: 23%
- Gemcitabine + RTE: 31.6%
- Vinorelbine, MMC, h GCSF: 11%

- Breast: 14.6%
- Hodgkin: 0.8%
- Lung cancer: 5.4%

All are probable underestimates

- Underreporting
- Subclinical involvement
  - Chemotherapy
  - Amiodarone pulmonary toxicity
  - Longterm cancer survivors

Subclinical effects

- **Rivera 2009**
  - 87 patients
  - Gemcitabine plus carboplatin, paclitaxel, or cisplatin
  - Volumes/flows: no significant change
  - DLCO: -8.7% pred (-10% baseline)
  - Clinical pulmonary toxicity: n=1 (1.1%)
- **Cerfolio 2009**
  - 132 patients
  - No change in lung volumes
  - DLCO -6.4%
  - Drop in DLCO >8% predicted major postoperative respiratory morbidity

- **Leo 2010**
  - 10 patients cisplatin + gemcitabine
    - Diffuse lung damage in 8
    - Postoperative pulmonary complications 6/10
  - *vs.* 10 nonchemo controls
    - Diffuse lung damage 0/10
    - Postoperative pulmonary complications 0/10

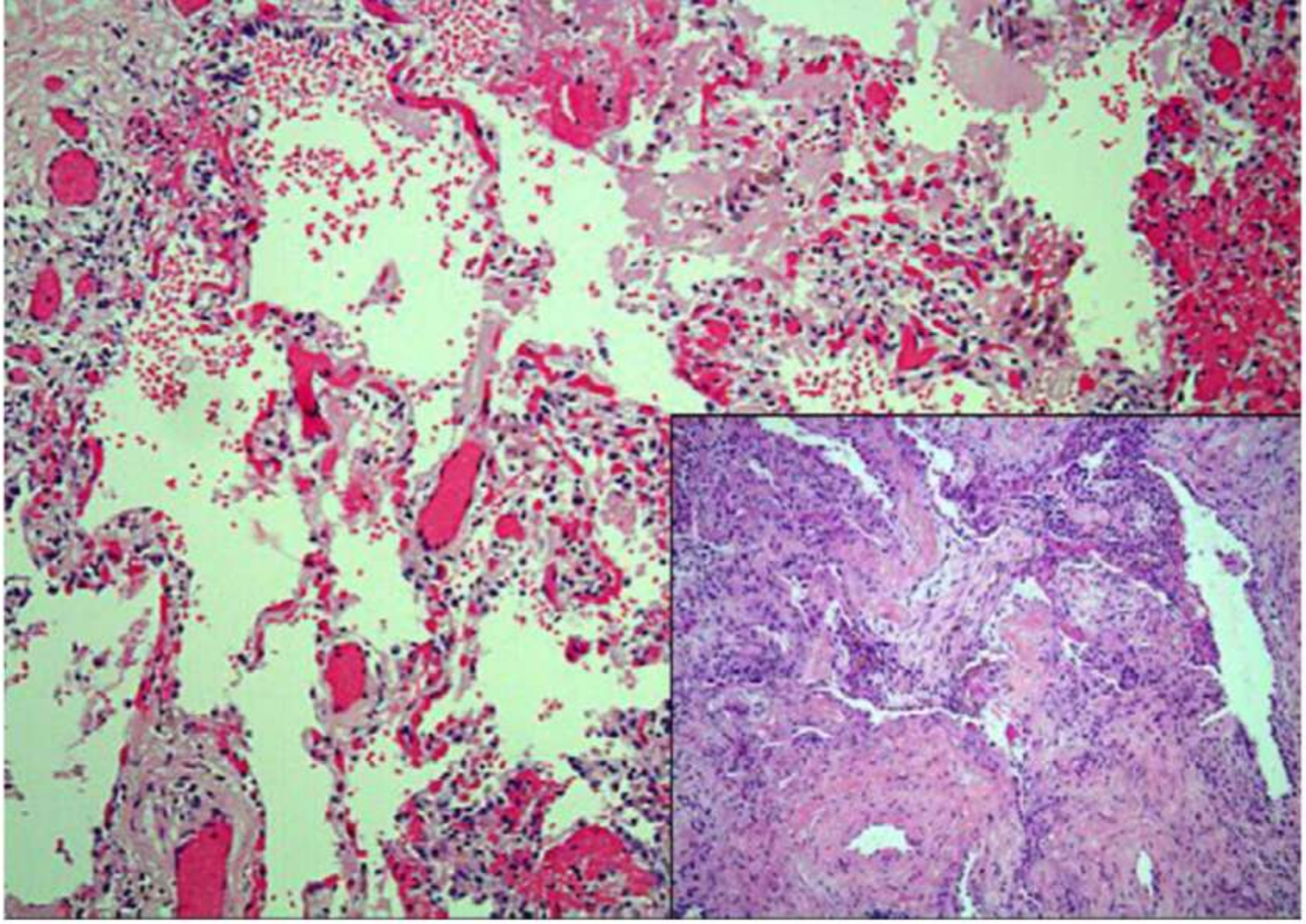
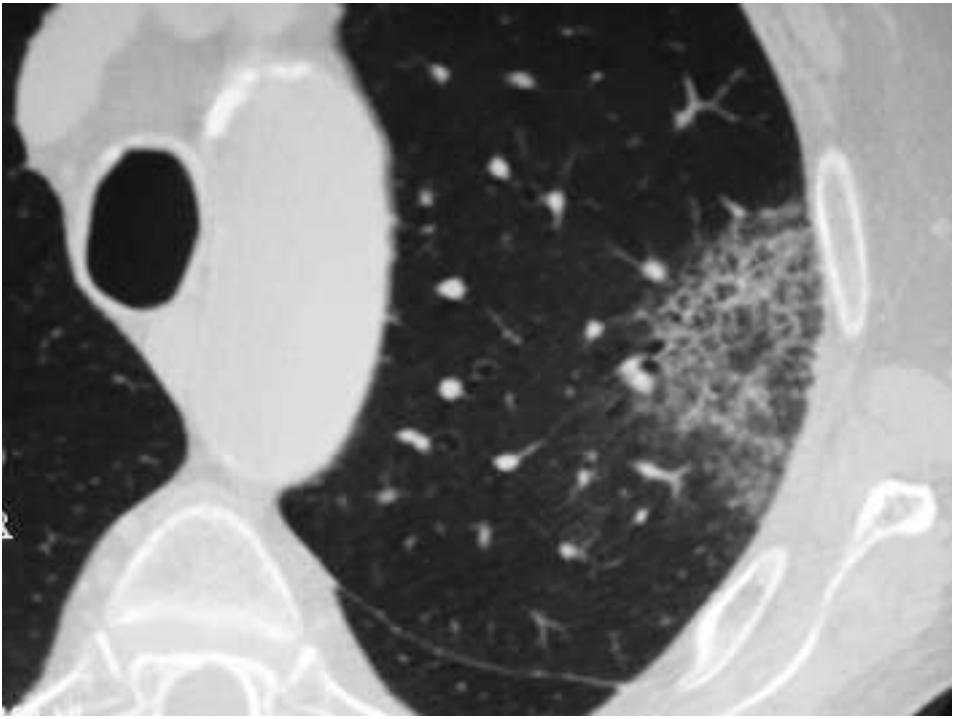
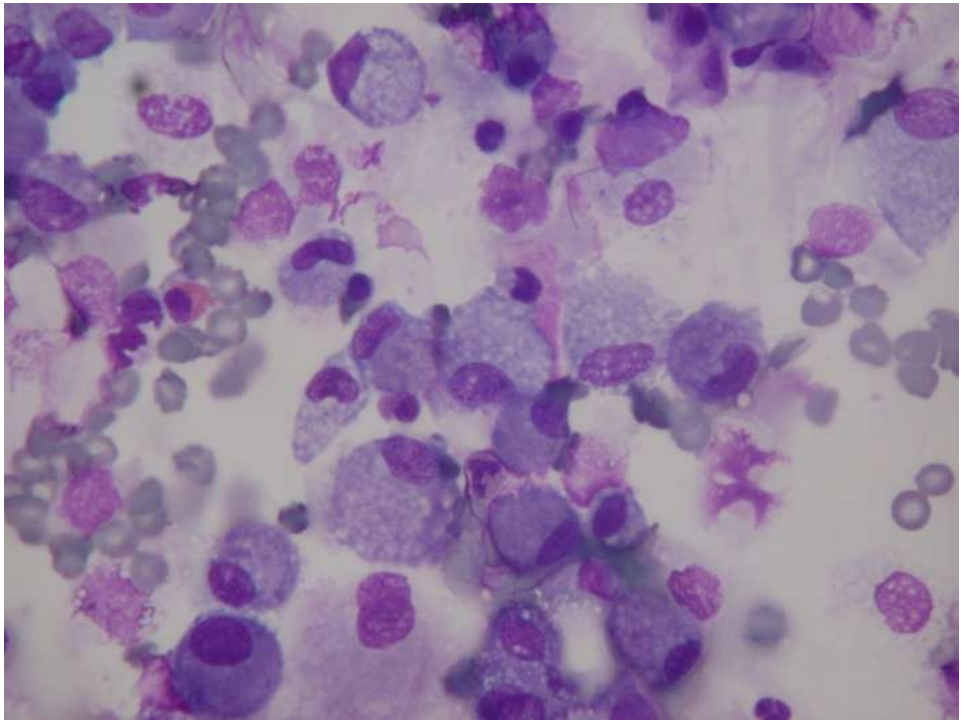


Fig. 2. Diffuse alveolar damage (DAD): interstitial and alveolar oedema and/or fibroblastic proliferation in association with epithelial and endothelial damage and alveolar fibrin laminar accumulation in the form of hyaline membranes.





By patterns

- **ARDS: 9.5%-13.6%**
- **DAH: 11-18%**
- **OP: 28%**
- **PIE: 10-18%**
- **PIE children: 18.2%**
- **A BAL with increased eosinophils: 12%**
- **TRALI: 1/5000; 10% fatal**

- **AAA: 14%**

The 2013 ATS/ERS classification

- **Major idiopathic interstitial pneumonias**
  - Idiopathic pulmonary fibrosis **Y**
  - Idiopathic nonspecific interstitial pneumonia **Y**
  - Respiratory bronchiolitis–interstitial lung disease **y**
  - Desquamative interstitial pneumonia **y**
  - Cryptogenic organizing pneumonia **Y**
  - Acute interstitial pneumonia **Y**
- **Rare idiopathic interstitial pneumonias**
  - Idiopathic lymphoid interstitial pneumonia **y**
  - Idiopathic pleuroparenchymal fibroelastosis **Y**
- **Unclassifiable idiopathic interstitial pneumonias** **Y**

- Pulmonary fibrosis
- NSIP (cellular > fibrotic)
- Eosinophilic pneumonia & AEP
- BOOP, AFOP
- Diffuse alveolar damage - ARDS
- Pulmonary edema
  (Cardiac, noncardiogenic, TRALI, ATRA)
- ILD with a granulomatous component
- Amiodarone pulmonary toxicity

DI pulmonary fibrosis (72 drugs)

- **Background influence of cigarette smoking (SRIF)**
- **Onset**
  - De novo (amiodarone)
  - Following subacute or acute DI-pneumonitis (bleo, chemo)
- **Localizes**
  - Bases or diffuse
  - Irradiated area
- **Progression**
  - Slow: amio, cyclophosphamide, nitrofurantoin
  - Rapid: bleo, paraquat, TNF antagonists

Available on the App Store

BROWSE NEWS ABOUT CONTACT

The Drug-Induced Respiratory Disease Website

Philippe Camus 2012- v2
Pascal Foucher - Philippe Camus 1997- v1
Department of Pulmonary Medicine and Intensive Care University Hospital Dijon France
Contribution: Ph Bonniaud, N Baudouin, A Fanton, C Camus, N Favrolt, M Guerriaud, L Jacquet

BROWSE BY » DRUGS PATTERNS

List All A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

ACE inhibitors (ACEI) I.b I.c IV.a IV.d V.a V.b V.d VIII.a VIII.q IX.e X.d XVIII.k — 5

ATRA I.b I.k II.a II.b II.f II.k III.a V.a V.m VI.a VI.d XII.c — 4

Abacavir I.a I.f II.a II.b IV.d X.a XV.d — 2

Abciximab III.a X.f — 3

Acebutolol I.b I.d V.a V.d — 2

SEARCH

Search by keyword

Advanced search

NOTE LEGEND ?

LEGEND PATTERNS ?

LATEST NEWS

Wed, 12 Jun 2013 09:28:47
Alerts - Warnings

Sun, 26 May 2013 17:55:11
To our pathology colleagues

Tue, 14 May 2013 10:27:01
Diagnosing DIRD

Wed, 20 Feb 2013 16:42:42

BROWSE BY » DRUGS PATTERNS

List All | I | II | III | IV | V | VI | VII | VIII | IX | X | XI | XII | XIII | XIV | XV | XVI | XVII | XVIII | XIX | XX

SEARCH

Search by keyword

Advanced search

I Interstitial/parenchymal lung disease

a	Acute pneumonitis/ILD	78
b	Subacute pneumonitis/ILD	206
c	Pulmonary infiltrates and eosinophilia (PIE) - Eosinophilic pneumonia	157
d	Organizing pneumonia (OP/BOOP)	90
e	Acute eosinophilic pneumonia (AEP)	26
f	Acute fibrinous organizing pneumonia (AFOP)	7
g	Pulmonary fibrosis	72
h	Subclinical parenchymal opacities	12
i	Diffuse pulmonary calcification	5
j	Exogenous lipoid pneumonia	12

Causative drugs

Adalimumab

I.a I.b I.g I.w II.b IV.a V.m IX.j X.b X.k XV.e XVII.b
XVII.e XVII.f XVII.g

1

Amiodarone

I.a I.b I.c I.d I.f I.g I.h I.k I.l I.r I.s I.u
I.w I.z II.b II.l III.a III.c IV.a IV.d IV.r V.a V.c V.d
VIII.a IX.d X.d X.f XI.c XI.f XII.a XII.c XII.n XV.a XV.b XV.c
XV.d XV.f XV.g XV.h XV.j XV.k XV.m XV.o XV.r XV.ao XVI.b XVI.i
XVI.n XVI.s XVI.aa XVI.ab XVIII.g XVIII.p XIX.a XIX.b XIX.e XIX.f XIX.m

3

Antithymocyte globulin (ATG-ALG)

I.g II.a II.b II.j

1

Aurothiopropanosulfonate

I.a I.b I.c I.d I.g IV.c XV.a

1

Azathioprine

I.a I.b I.c I.d I.g I.l I.ah II.b III.a VIII.a X.g X.o
XV.a XV.f XV.j XVII.e

1

Bepridil

I.b I.g

-

Beta-blockers

I.a I.b I.c I.d I.g I.u II.a IV.a IV.f V.a V.c V.d
VI.w IX.d X.d X.y XI.r XII.m

1

Bleomycin

ORIGINAL ARTICLE

Chronic Nitrofurantoin–Induced Lung Disease

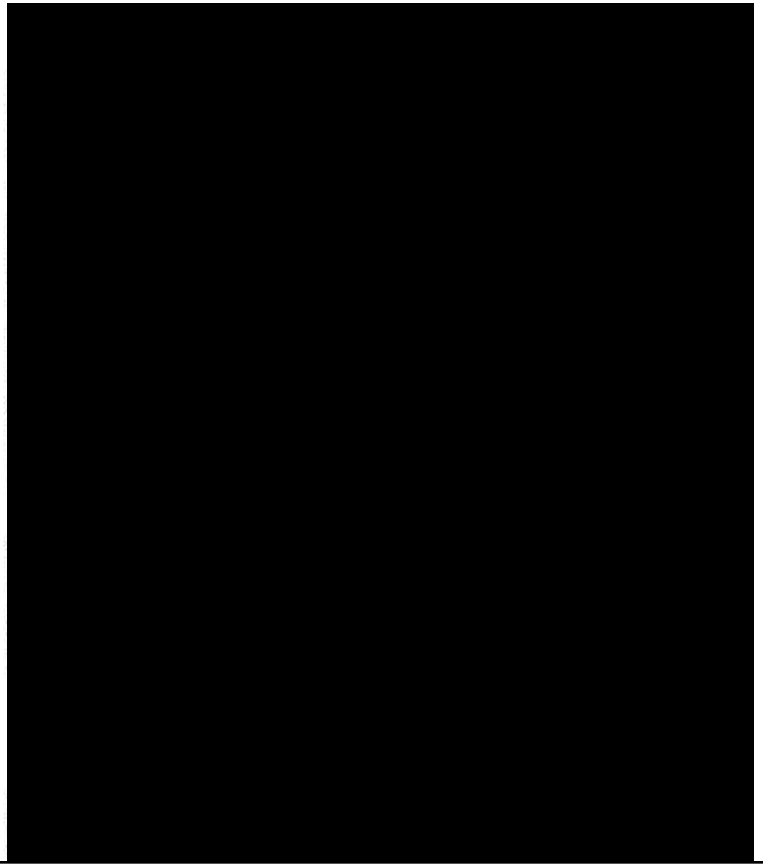
JOSE L. MENDEZ, MD; HASSAN F. NADROUS, MD; THOMAS E. HARTMAN, MD; AND JAY H. RYU, MD

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

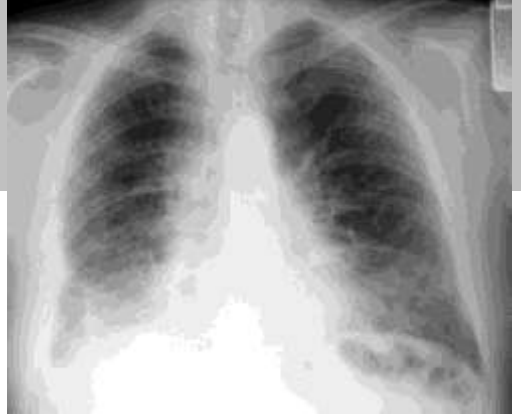
PATIENTS AND METHODS: **We retrospectively reviewed the medical records of 18 patients with chronic nitrofurantoin–induced lung disease who were seen at the Mayo Clinic in Rochester, Minn, from January 1, 1997, to December 31, 2002.**

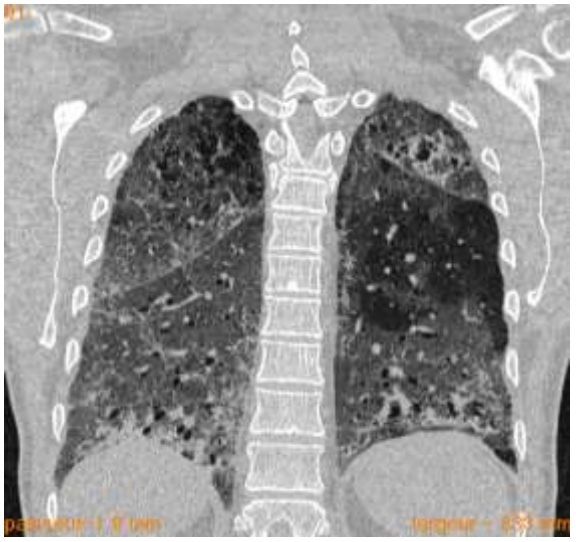
RESULTS: **The median age of the 18 patients was 72 years (range, 47-90 years) at the time of diagnosis; 17 (94%) were women. Onset of symptoms occurred after a median interval of 23 months (range, 10-144 months) following the initiation of nitrofurantoin therapy for the prevention of recurrent urinary 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.**

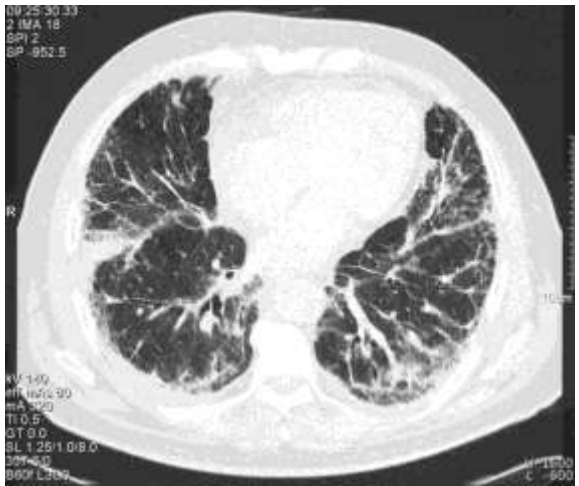
CONCLUSIONS: **Chronic nitrofurantoin–induced lung disease is seen predominantly in older women who present with respiratory symptoms after a year or more of nitrofurantoin therapy. Associated radiological features are relatively nonspecific but usually include bilateral areas of ground-glass opacities 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.**



- 18 patients 17W
- Average time of onset: 23 months
- Time to diagnosis: 4 months
- Eosinophilia: 17%
- Lung biopsy: NSIP + fibrosis, OP giant cells
- Withdrawal: 18/18
- Steroids: 9/18
  - Improved: 16
  - Stable: 2
  - Residual disease 12







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?

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Gupta and Trautner suggest using nitrofurantoin as prophylaxis for recurrent urinary tract infections (UTIs) in non-pregnant women.[1] They mention the risk of pulmonary toxicity ("nitrofurantoin lung") associated with prolonged treatment but suggest that this occurs after years of treatment.

In Grampian we have identified 13 patients in the past four years with nitrofurantoin lung, 12 of whom were non-pregnant women receiving prophylactic treatment for recurrent UTI. Ten of them had been treated with nitrofurantoin for 18 months or less before diagnosis (mean treatment duration 14 months). None had been aware of potential lung toxicity, and the prescribing clinicians were surprised by the diagnosis. All patients were advised to stop taking nitrofurantoin, and six also received empirical oral steroids. Serial spirometry (available in nine patients) showed dramatically improved lung function after nitrofurantoin was stopped (mean predicted forced vital capacity 78% at diagnosis, 110% after cessation); serial chest radiographs also showed improvement.

Data from Prescribing Information System for Scotland show that community prescribing of nitrofurantoin more than tripled from 2008 to 2012—from 3.4 to 11 prescribed items per 1000 patients. We believe this change in prescribing, advocated in current guidelines,[2 3] is reflected in our local experience and elsewhere in the UK.[4 5] We anticipate a continued increased in the incidence of nitrofurantoin lung and worry that many clinicians have forgotten the potential for lung toxicity.

Nitrofurantoin lung was initially misdiagnosed as cardiac failure, pneumonia, and, in one case, metastatic cancer. Patients should be advised to report any respiratory symptoms—such as worsening cough or breathlessness—that develop. Current guidelines and primary care prescribing systems should emphasise the potential for toxicity, which is reversible if the association is recognised early.

Competing interests: None declared.

1 Gupta K, Trautner BW. Diagnosis and management of recurrent urinary tract infections in non-pregnant women. *BMJ* 2013;346:f3140. (29 May.)
2 Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;52:e103-20.
3 Health Protection Agency. Management of infection guidance for primary care for consultation and local adaptation. 2012. www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1279888711402.
4 Madani Y, Mann B. Nitrofurantoin-induced lung disease and prophylaxis of urinary tract infections. *Prim Care Respir J* 2012;21:337-41.
5 Weir M, Daly GJ. Lung toxicity and nitrofurantoin: the tip of the iceberg? *QJM* 2013;106:271-2.

Cite this as: *BMJ* 2013;346:f3897

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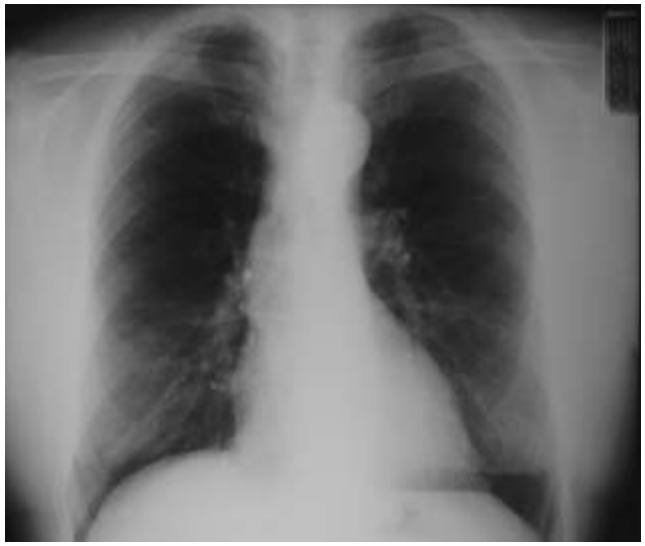
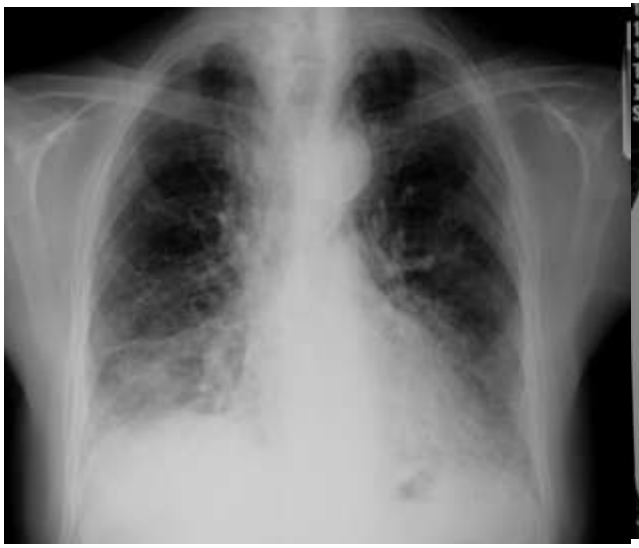
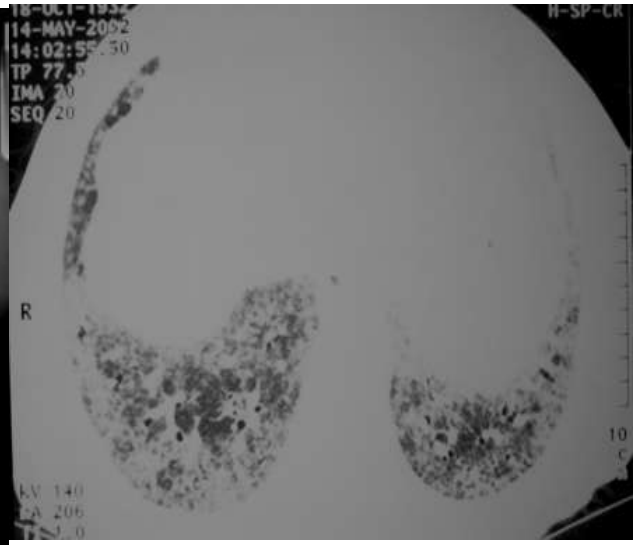
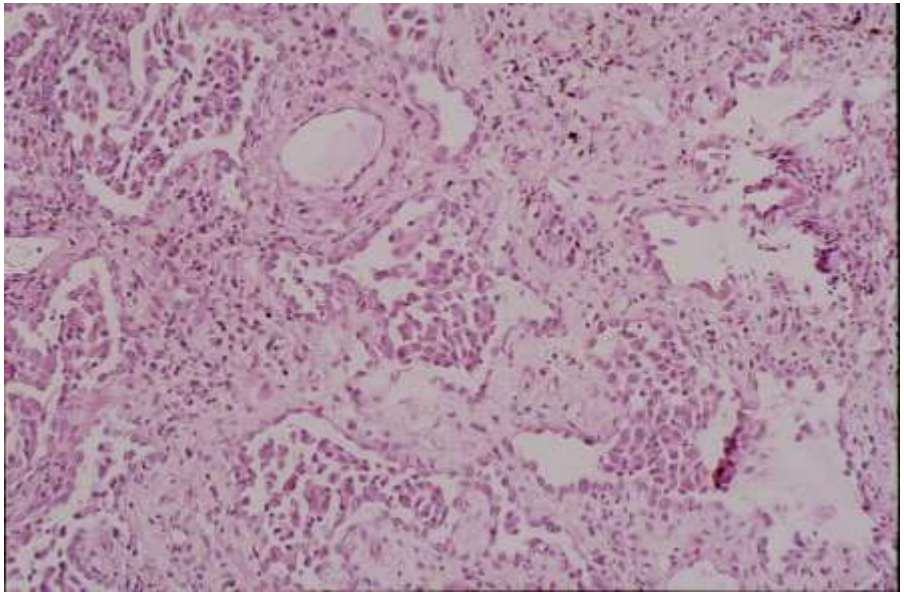
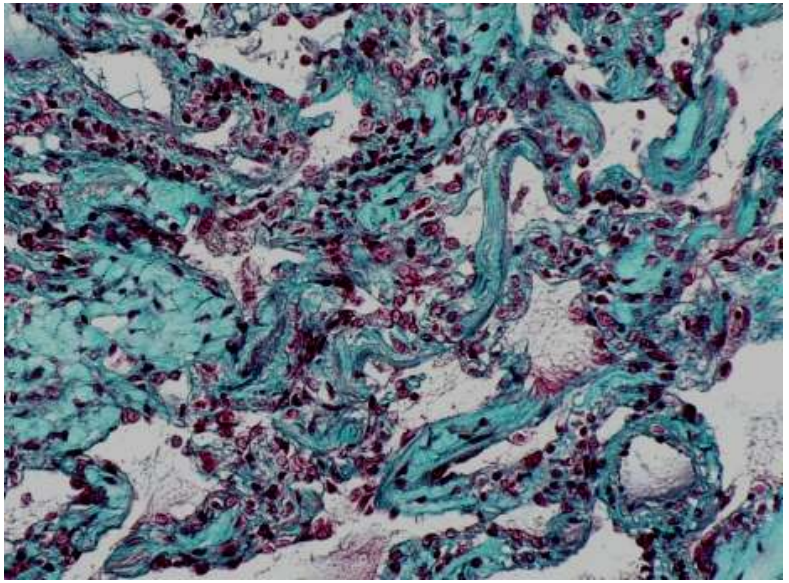
Amiodarone-induced fibrosis



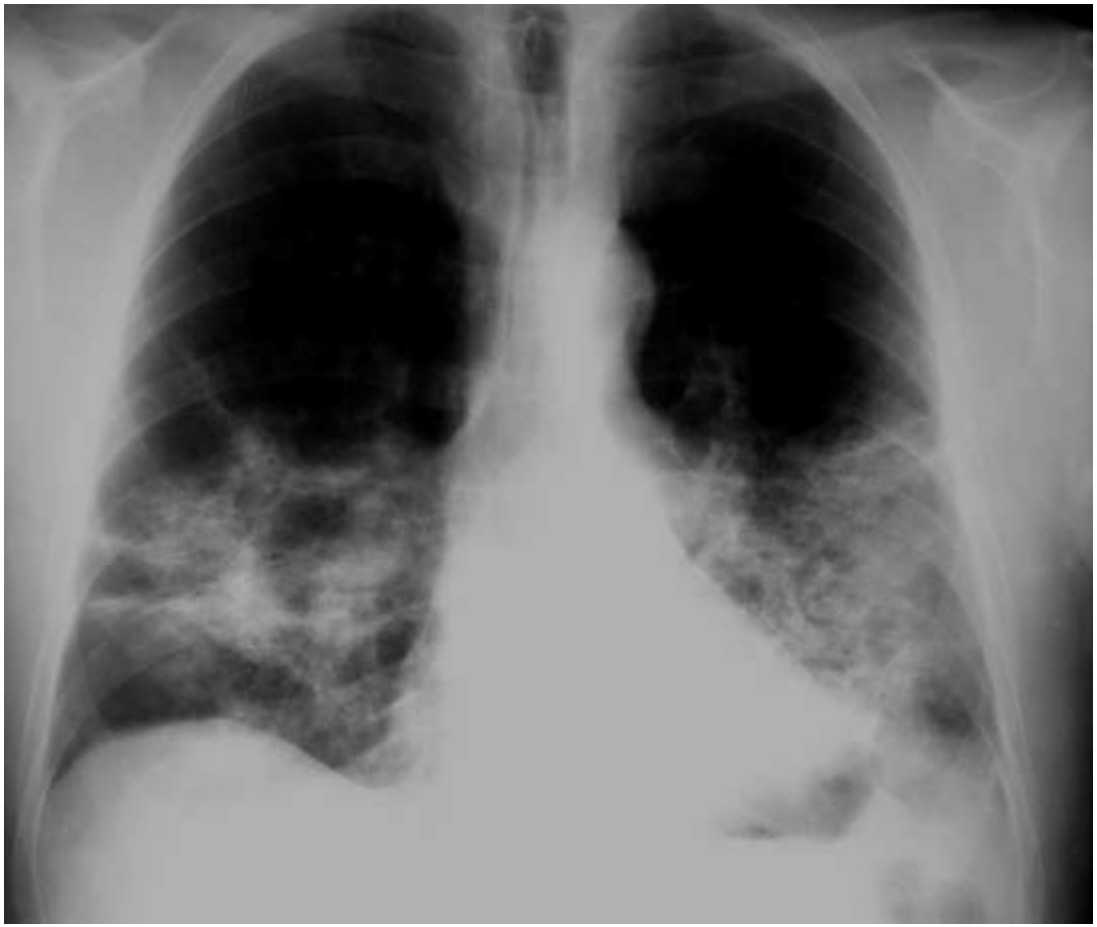


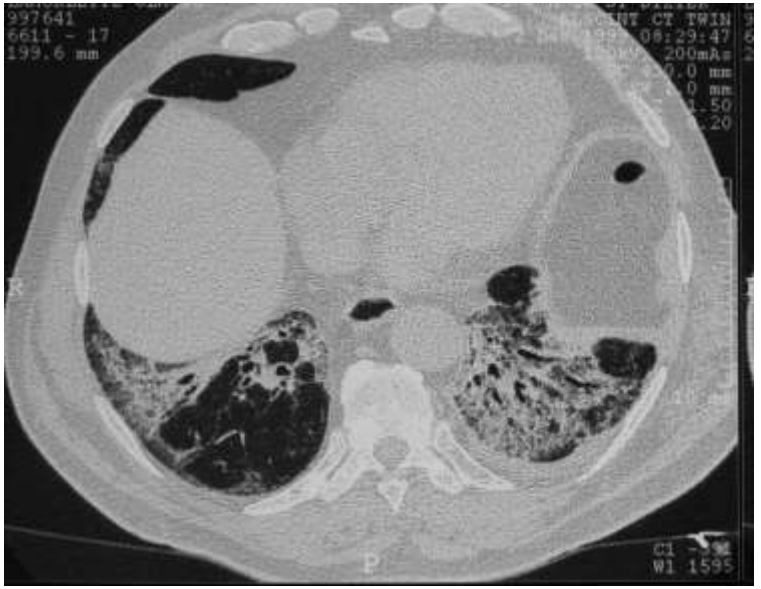


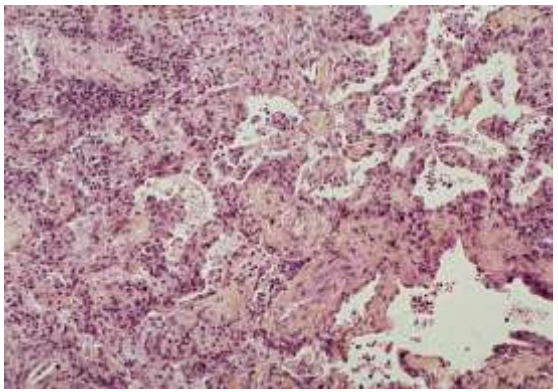




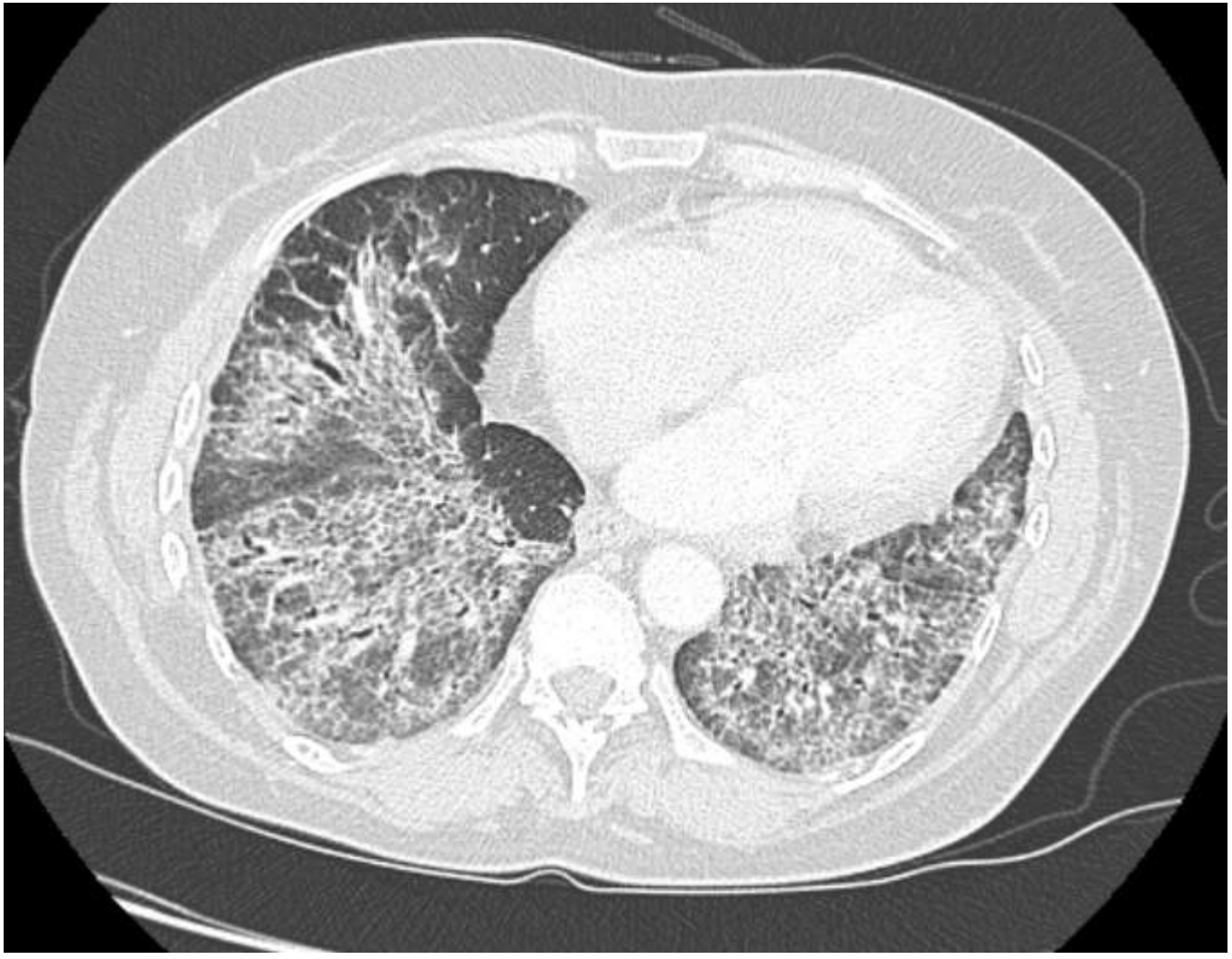
- Fibrosis as a late pattern of chemotherapy lung
  - Bleomycin, busulfan, cyclophosphamide, MMC, nitrosourea

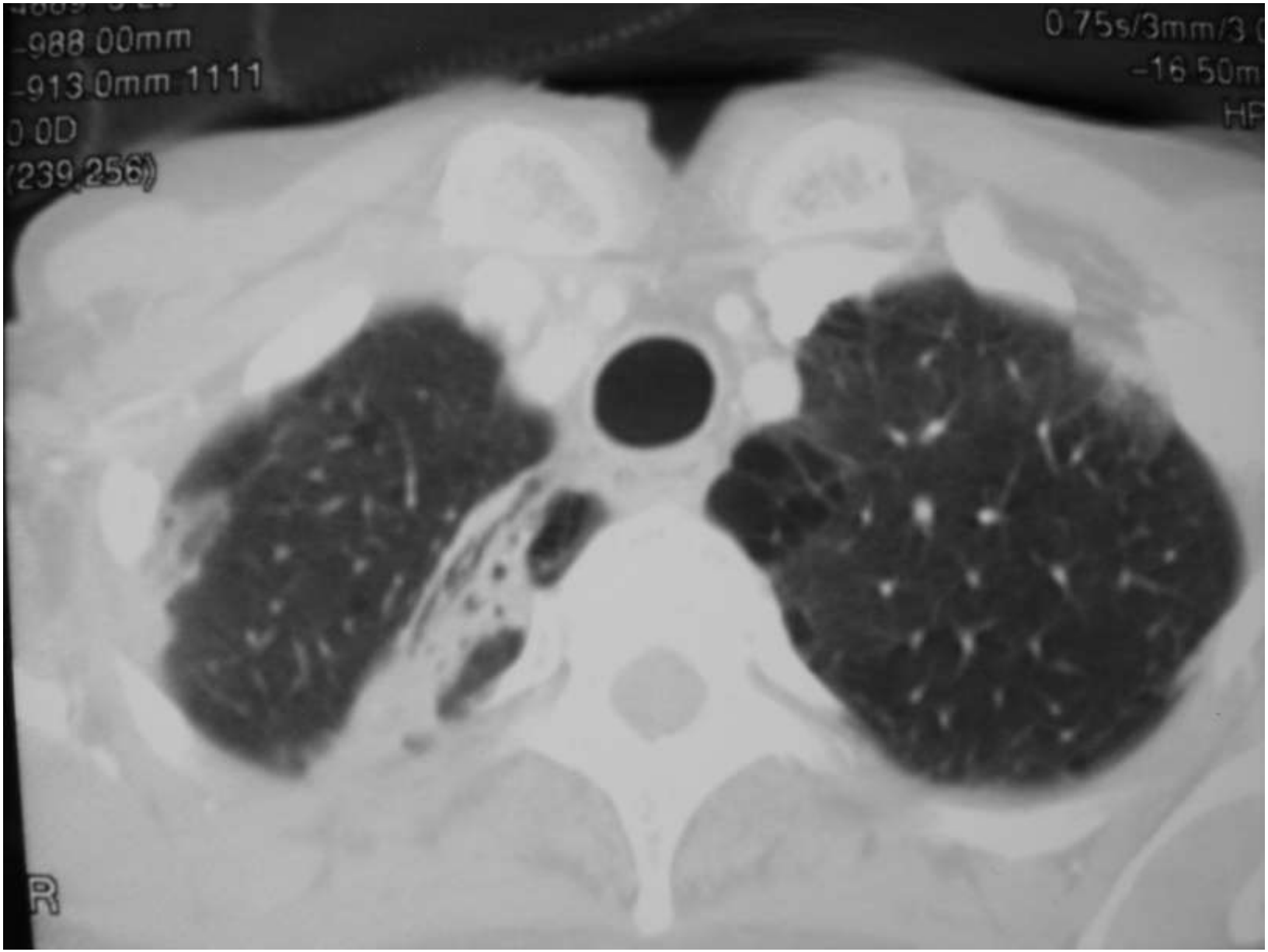






- Post-MTX pneumonitis in RA

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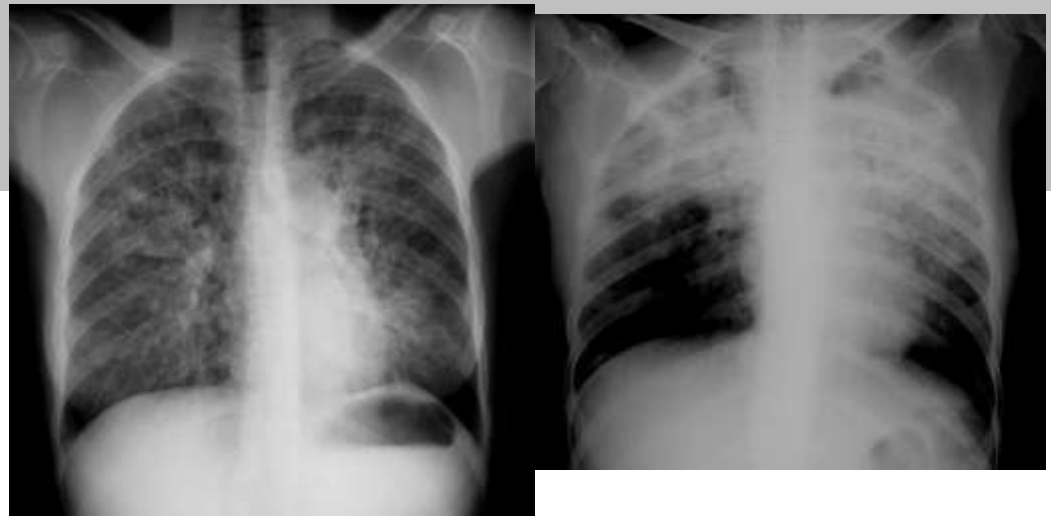
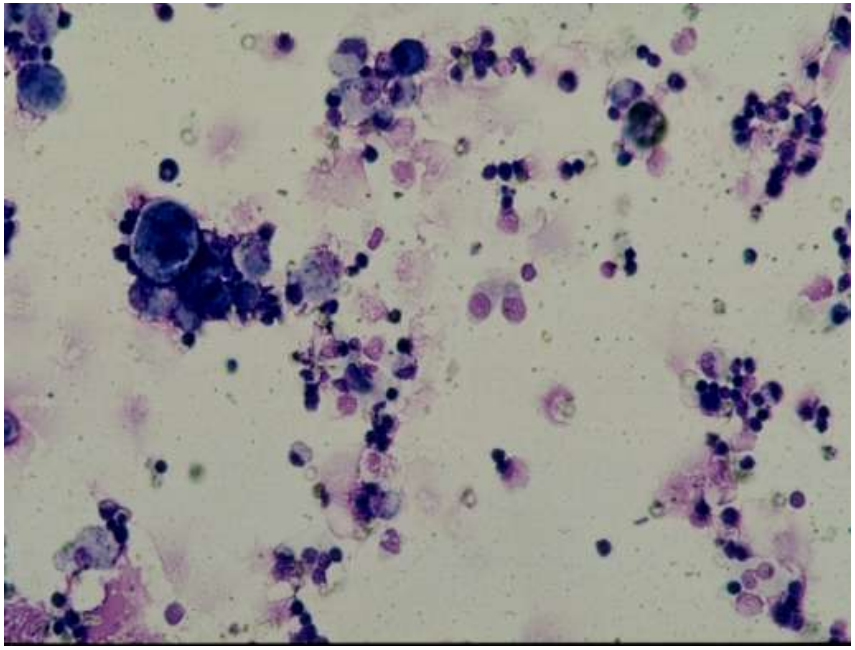
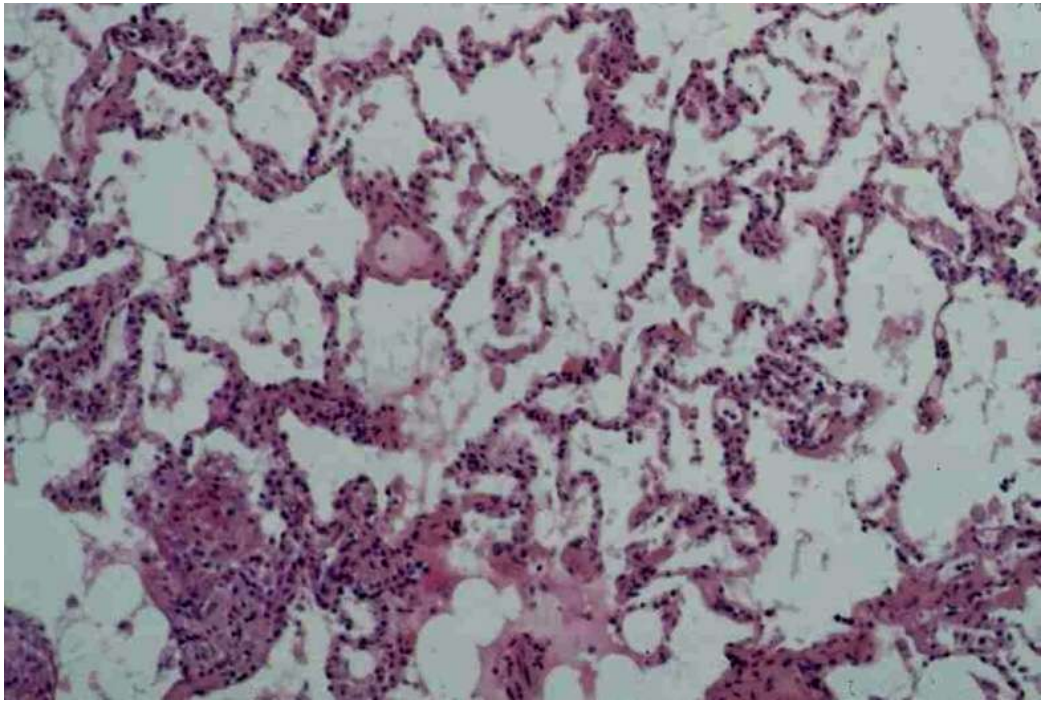
0.75s/3mm/3
-16.50m
HF
R

DI-NSIP (250 drugs)

- Common
- Cellular ILD

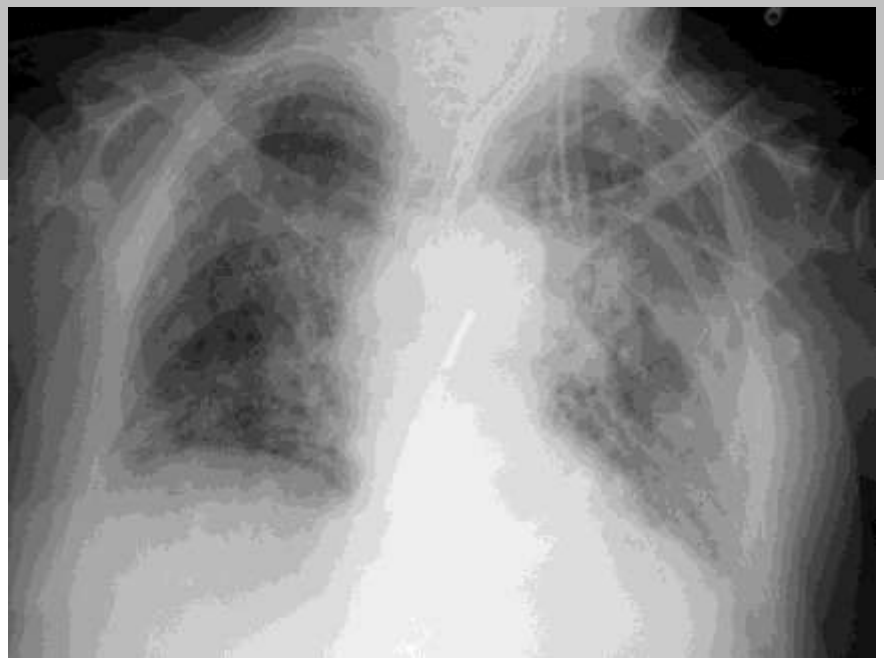


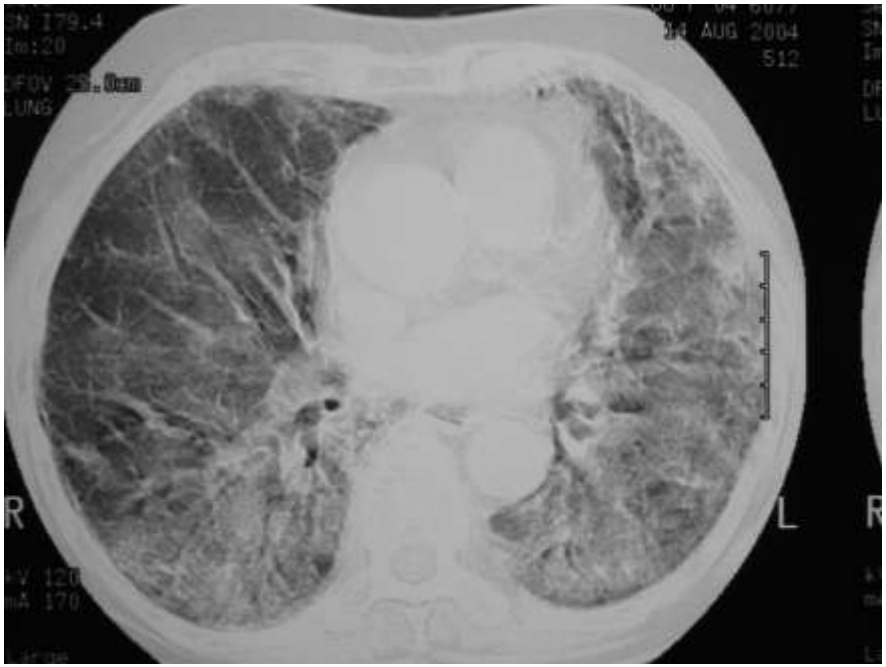




- Causal drugs: cyclophosphamide, flecainide, fludarabine, lefunomide, methotrexate, m-TOR inhibitors, nitrofurantoin, TKI
- BAL unpredictable (D'Elia 2014) 47 cases
  - Ly 21%, LN 23%, LE 21%, LNE 23%, N 9%
  - Rule out *Pneumocystis*
- Rechallenge -> relapse, sometimes fatal
- Pneumotox database
  - Rechallenge 549 papers
  - With relapse 328
  - Without relapse 88

- Acute NF pulmonary toxicity
  - <2 weeks
  - Chest pain, fever, cough breathlessness
  - Pleural effusions
  - Mild peripheral eosinophilia
  - Resolves with cessation
  - Relapses with reexposure



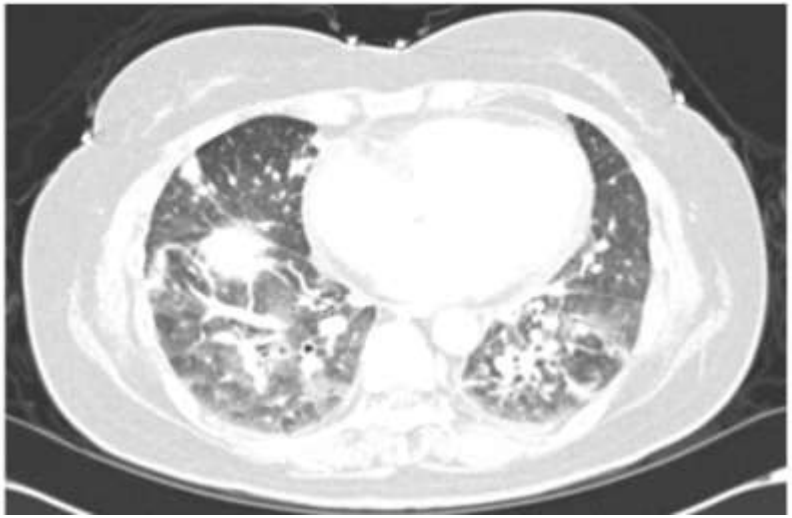


Successful Erlotinib Rechallenge After Erlotinib-Induced Interstitial Lung Disease

Jennifer L. Dallas, MD, Michael A. Jantz, MD,† Judith L. Lightsey, MD,‡ Christopher Sonntag, MD,§ and Frederic J. Kaye, MD**

CASE REPORT

A 56-year-old nonsmoking Korean woman was diagnosed with stage 4 lung adenocarcinoma. Computed tomography (CT) scan showed a dominant left lung mass (Figure 1) with pulmonary, mediastinal, liver, adrenal, bone, and brain metastases. Erlotinib 150 mg daily and whole brain irradiation were started, and an epithelial growth factor receptor (EGFR) exon 19 mutation was detected. Symptoms improved until week 5 when she developed a new fever, worsening skin rash, and nonproductive cough. Erlotinib was held, and topical cleocin and oral doxycycline 200 mg daily were begun. Over the next 4 days, cough and dyspnea worsened with fall of O_2 saturation to 92%, prompting repeat CT scan. This revealed a tumor response; however, new extensive bilateral ground glass opacities consistent with erlotinib-induced interstitial lung disease (ILD) were noted (Figure 2). No further



CASE REPORTS

Successful reintroduction of methotrexate after pneumonitis in two patients with rheumatoid arthritis

N J Cook, G J Carroll

Abstract

Two patients are described with severe and progressive rheumatoid arthritis in whom methotrexate was reintroduced despite previous methotrexate related pneumonitis. In both patients a marked improvement in disease control occurred without a recurrence of the pneumonitis.

In the treatment of severe erosive arthritis, a limited number of disease modifying drugs are available. When all avenues of treatment have led to intolerance or inefficacy in the patient with progressive disease, the question arises as to whether a previously useful but poorly tolerated drug can be safely reintroduced. Factors influencing this decision include the nature of the toxicity previously encountered, the severity of the patient's disease, and the current state of knowledge with respect to the agent in question.

We report here two patients with methotrexate pneumonitis in whom the drug was subsequently reintroduced and in whom pneumonitis did not recur.

Patients and methods

PATIENTS

For the purpose of diagnosis in this study, we used the criteria for methotrexate pneumonitis described by Searles and McKendry.[1]

METHODS

Gallium-67 scintigraphy was used to monitor the patients during rechallenge with methotrexate. This is a very sensitive but non-specific test for pulmonary inflammation which has been shown to correlate well with other indices of disease activity in inflammatory disorders of the lung, such as sarcoidosis and pulmonary fibrosis.[2-4] A ^{67}Ga scan may be abnormal before symptoms develop or before clinical or radiological signs are apparent.[5 6]

The ^{67}Ga index used was based on the method described by Line *et al*[2]; the maximum possible gallium index is 400 U and a scan is considered to be abnormal if the index is greater than 50 U.

Results

PATIENT 1

A 69 year old woman with a 40 year history of rheumatoid arthritis characterised by widespread joint erosion and high concentrations of rheumatoid factor and antinuclear antibodies was treated with methotrexate, 2·5 mg intramuscularly once a week, beginning in May 1983, and increasing to 7·5 mg a week over three months. Previous disease modifying drugs included gold salts, cyclophosphamide, sulphasalazine, D-penicillamine, azathioprine, and levamisole, all of which had been discontinued because of side effects or lack of efficacy. This patient was unable to tolerate prednisolone. Methotrexate was tolerated and its use was accompanied by marked symptomatic improvement.

In April 1985, she was admitted to her local hospital with a three week history of fever, malaise, dyspnoea, and dry cough. She had never smoked but had a past history of mild asthma controlled by regular use of salbutamol. Examination showed respiratory rate 35/minute, pulse rate 120/minute, blood pressure 140/80 mmHg, temperature 37·8°C (subsequently peaking at 38·1°C). Auscultation showed widespread pulmonary crepitations. A chest radiograph (fig 1) showed diffuse pulmonary infiltrates. Laboratory studies showed a haemoglobin concentration of 111 g/l, white cell count of $4{\cdot}5\times10^9$/l (neutrophils 76%, lymphocytes 16%, monocytes 8%), and an erythrocyte sedimentation rate of 22 mm/hour. No bacteria were cultured from three sets of blood cultures.

The patient was treated with intravenous ampicillin, gentamicin, and nebulised salbutamol. Her condition deteriorated and she was transferred to an intensive care unit where her arterial blood gas tensions were: P_{CO_2} 30 mmHg, P_{O_2} 48 mmHg on 14 l oxygen/min (pH

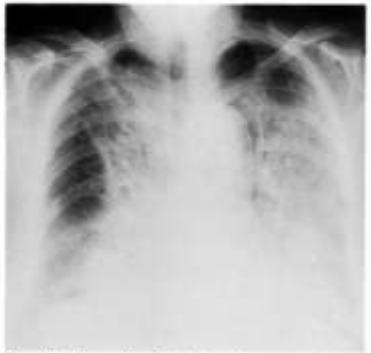


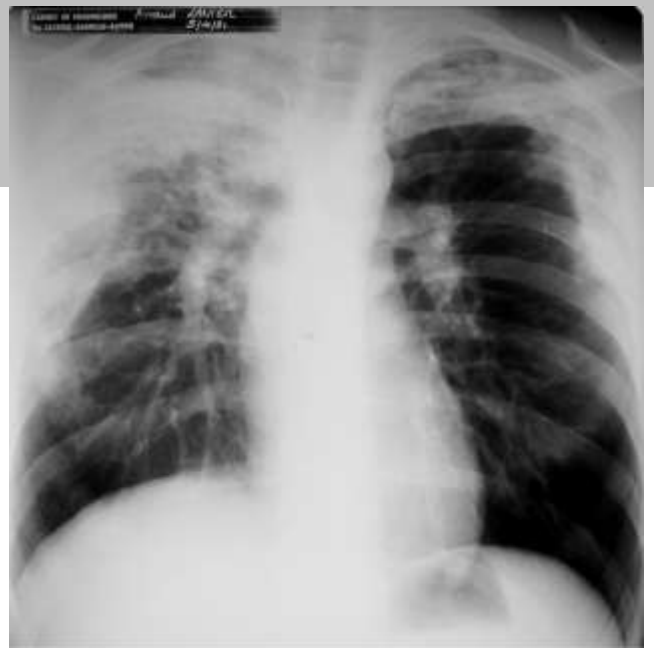
Figure 1 Chest radiograph of patient 1 on presentation in an erect position.

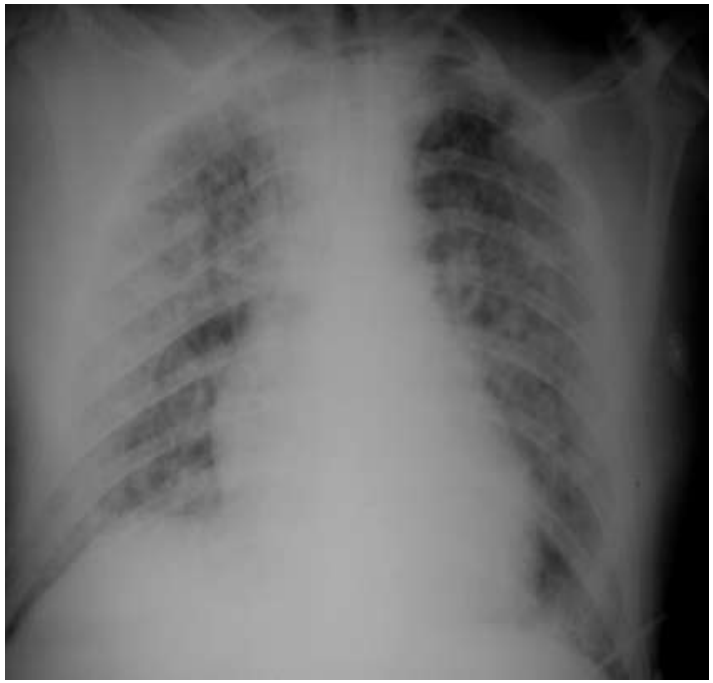
Department of Rheumatic Diseases, Royal Perth (Rehabilitation) Hospital, 6 Selby Street, Shenton Park, Perth, Western Australia 6008, Australia
N J Cook
G J Carroll

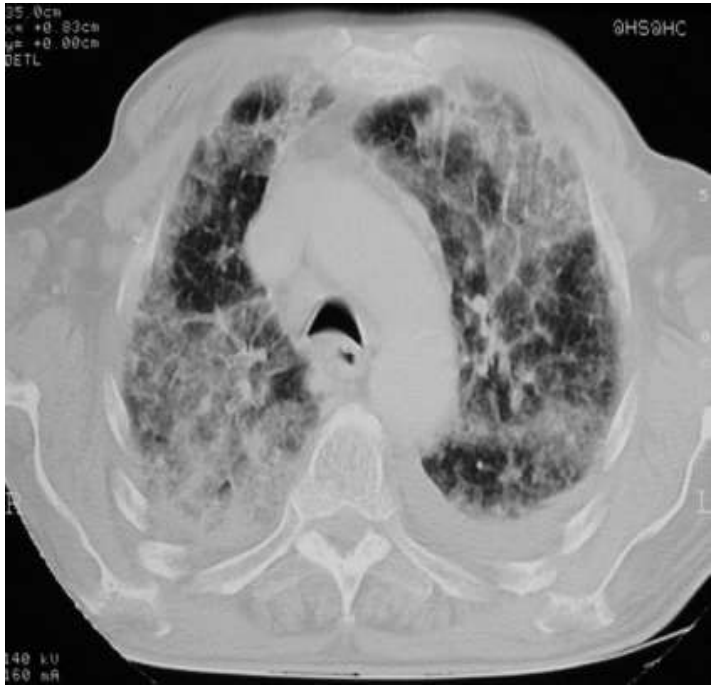
Correspondence to:
Dr Carroll.

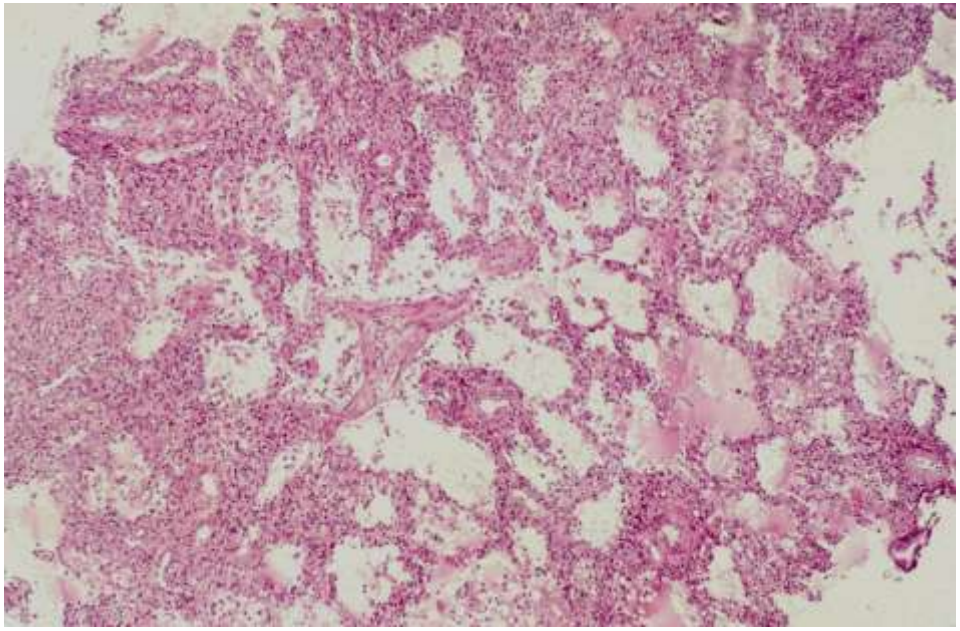
Accepted for publication
5 February 1991

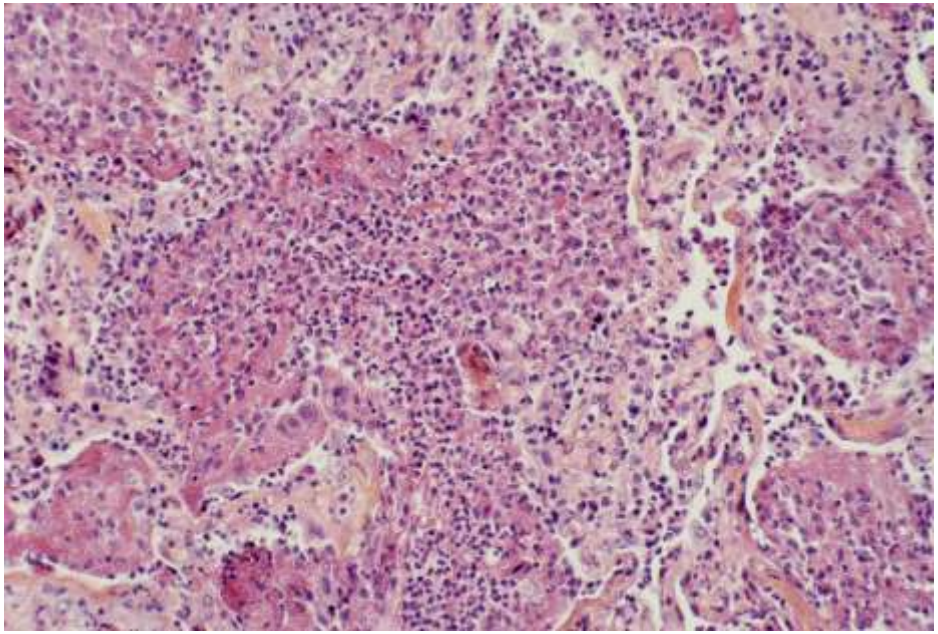
- Eosinophilic pneumonia
  - 157 implicated drugs
  - Antibiotics, NSAIDs
  - Eosinophils in blod, BAL, tissue
  - Relapses with rechallenge



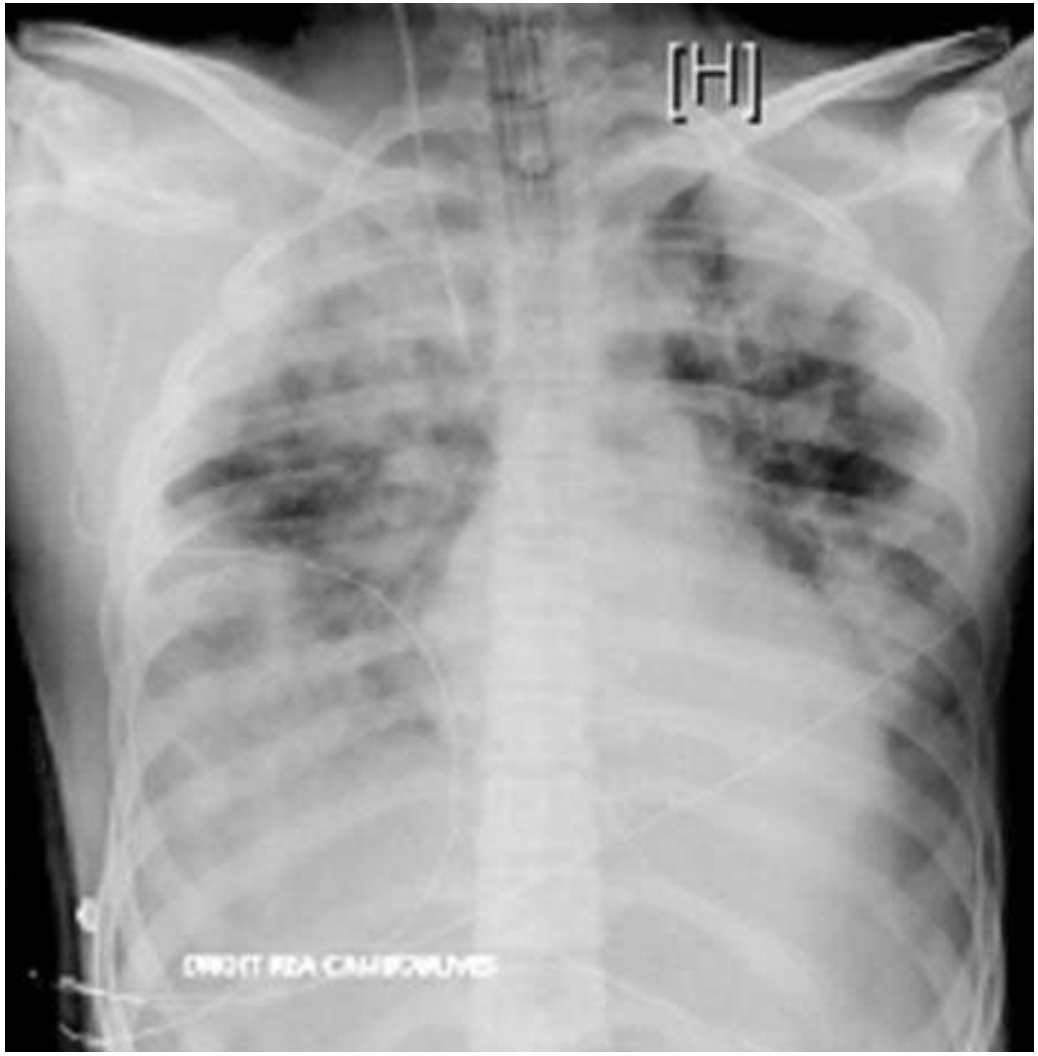




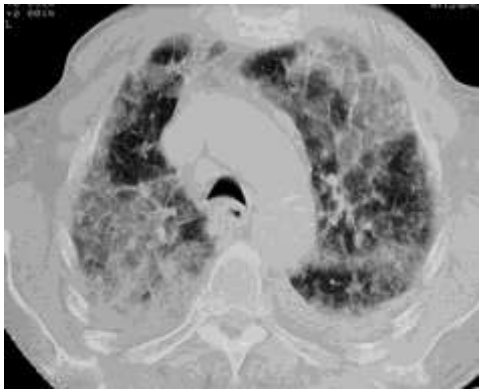


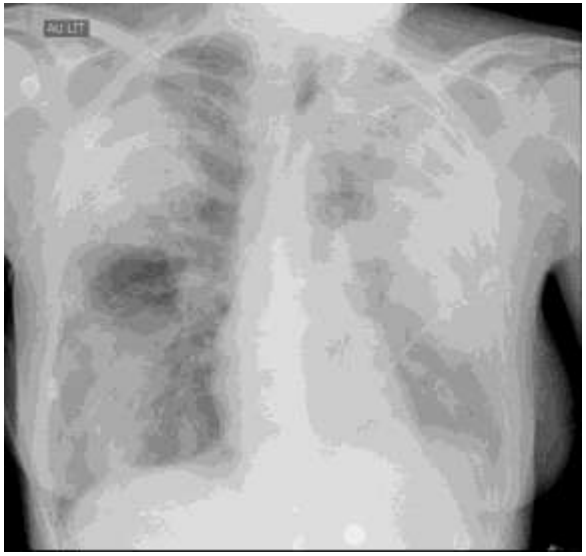


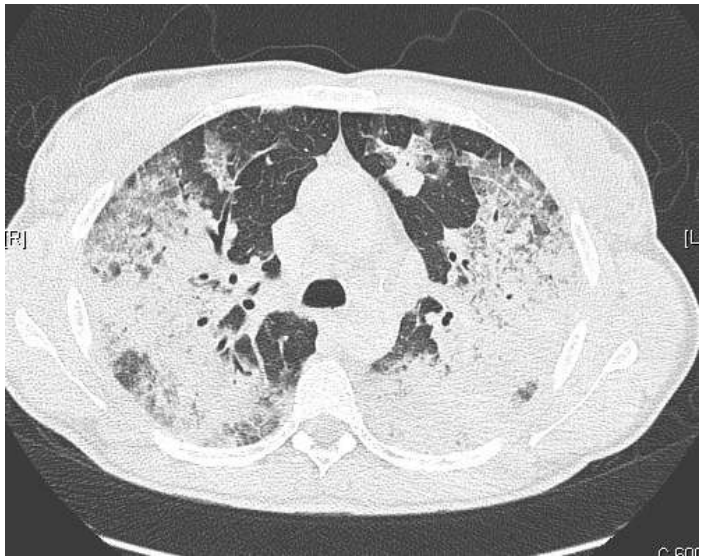
- **3-Substance-related**
  - **Adolescent boy**
  - **Cannabis & tobacco**
  - **Eosinophilia**
    - Blood 3,100/uL
    - BAL: 21%
  - **AEP**
  - **ECMO x48hrs**
  - **Extubated: day 5**



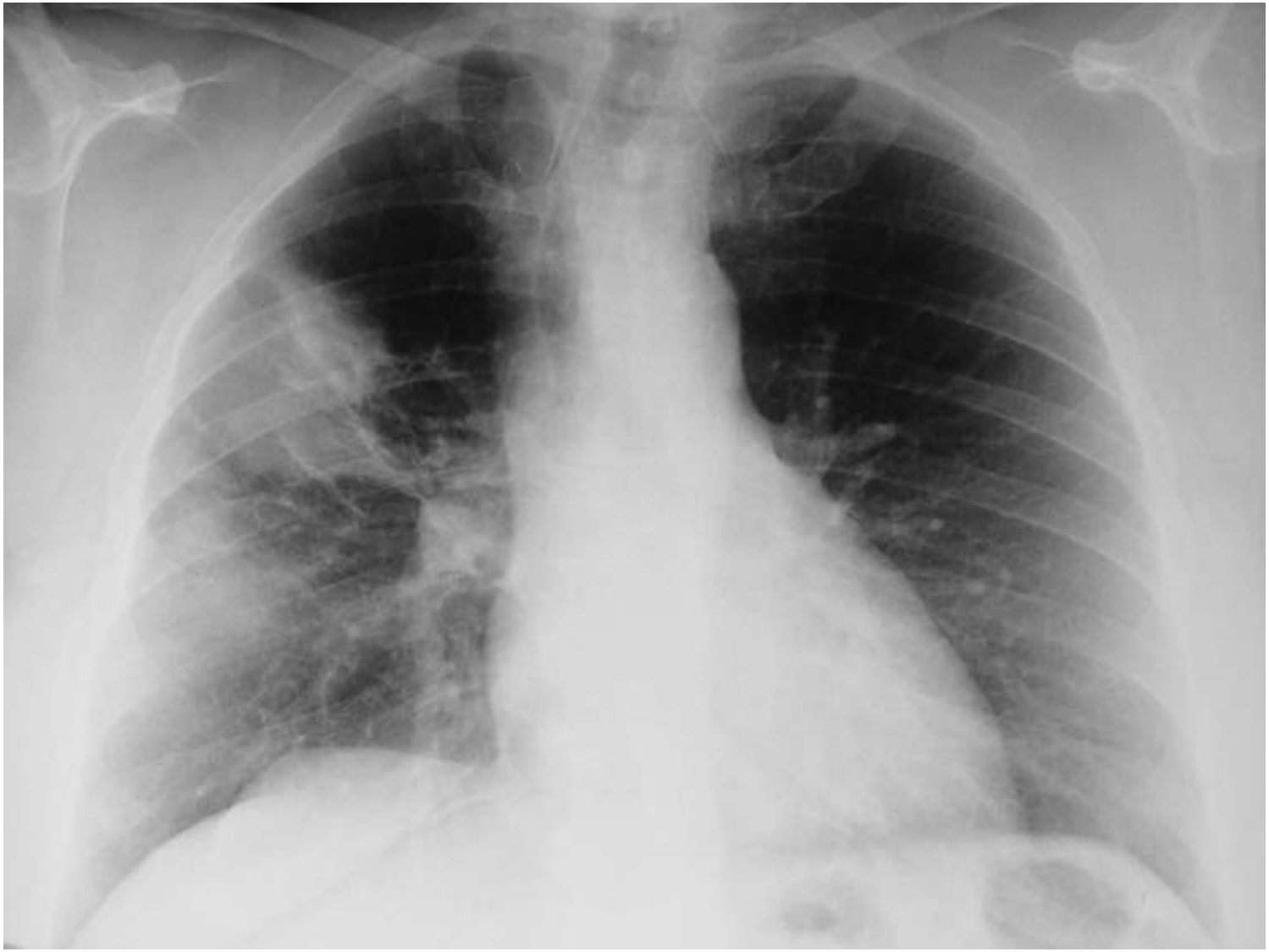
- **Acute eosinophilic pneumonia (AEP)**
  - Minocycline, daptomycine, sulfa, antidepressants, NSAIDs
  - Inhaled- tobacco smoke, cocaine, marijuana
  - Pleural effusion common
  - Eosinophilis in the BAL
  - MV can be required
  - Withdrawal + corticosteroids

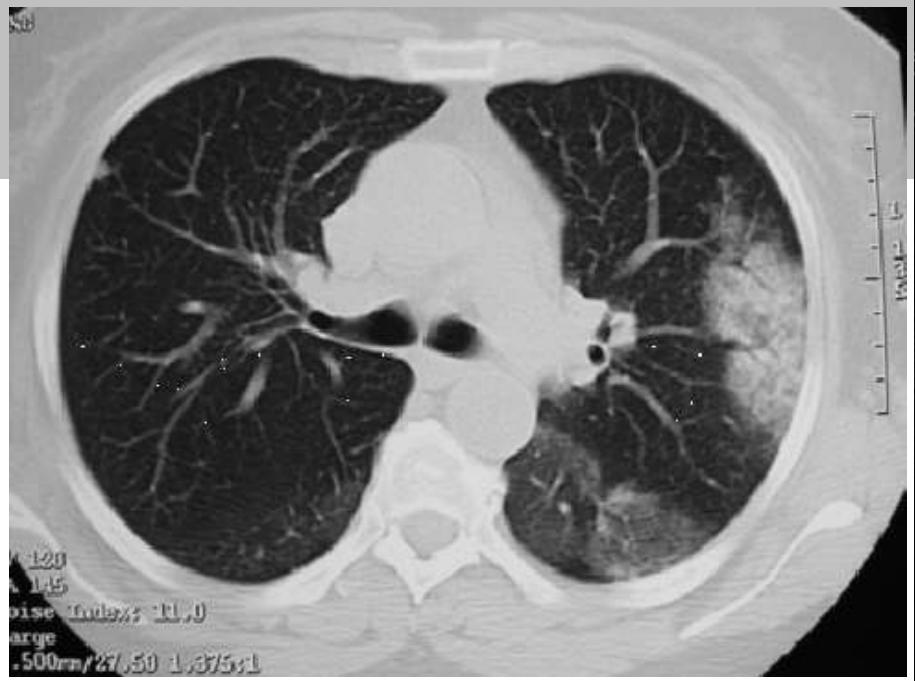


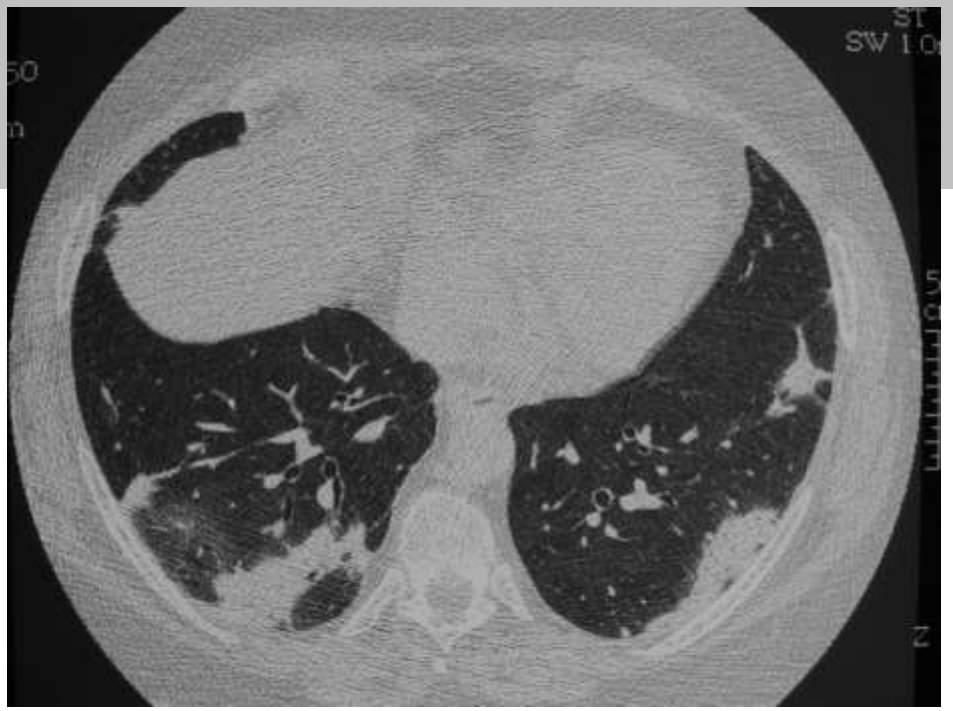


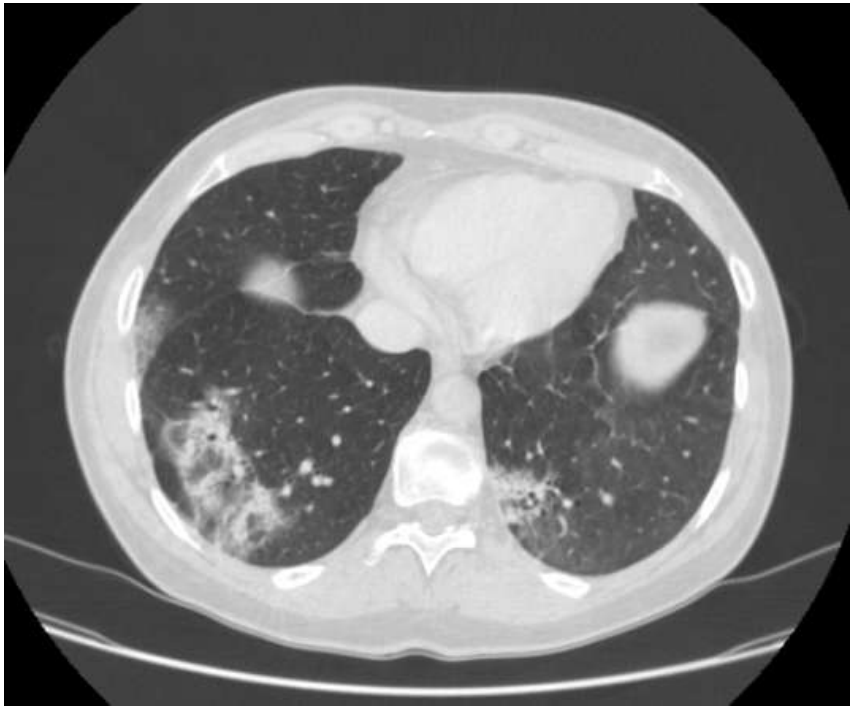


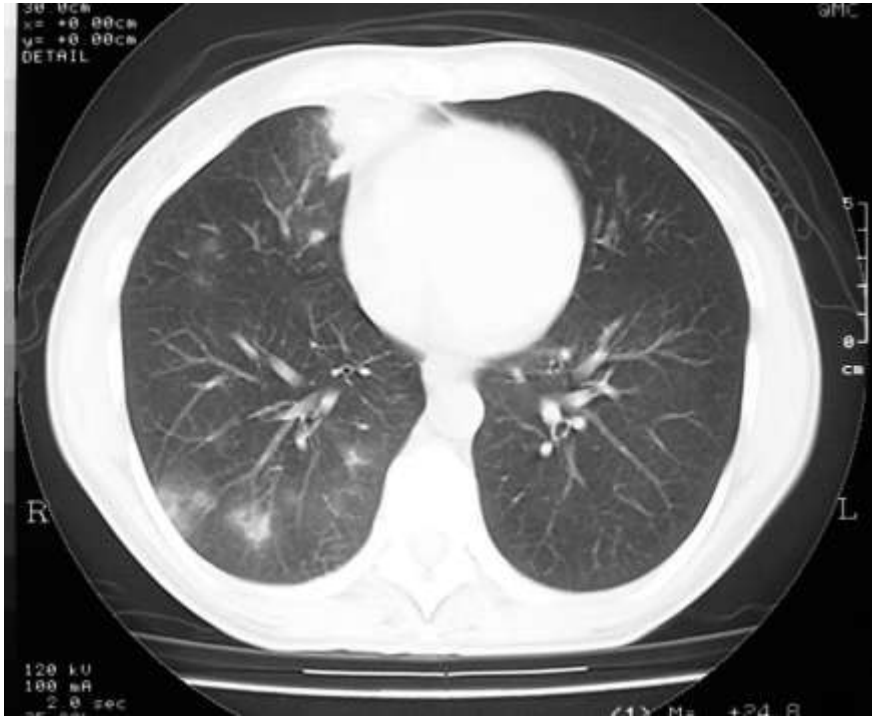
BOOP: 90 drugs










DETAIL
120 kV
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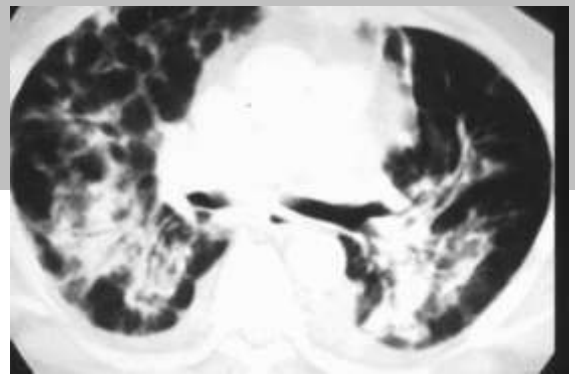
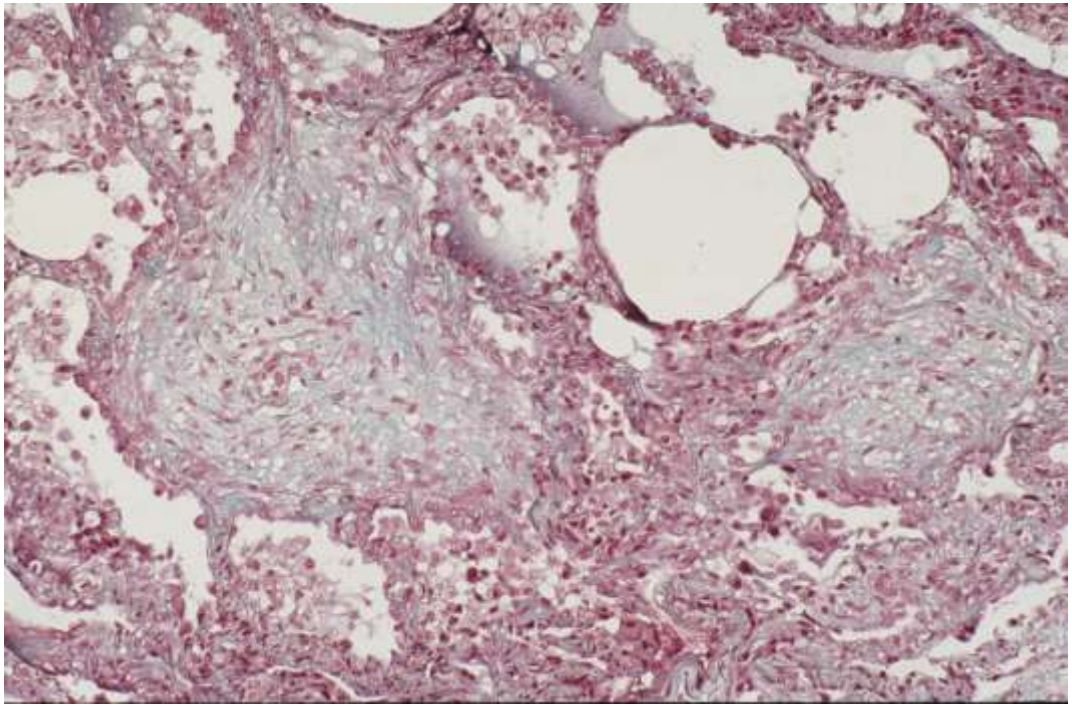
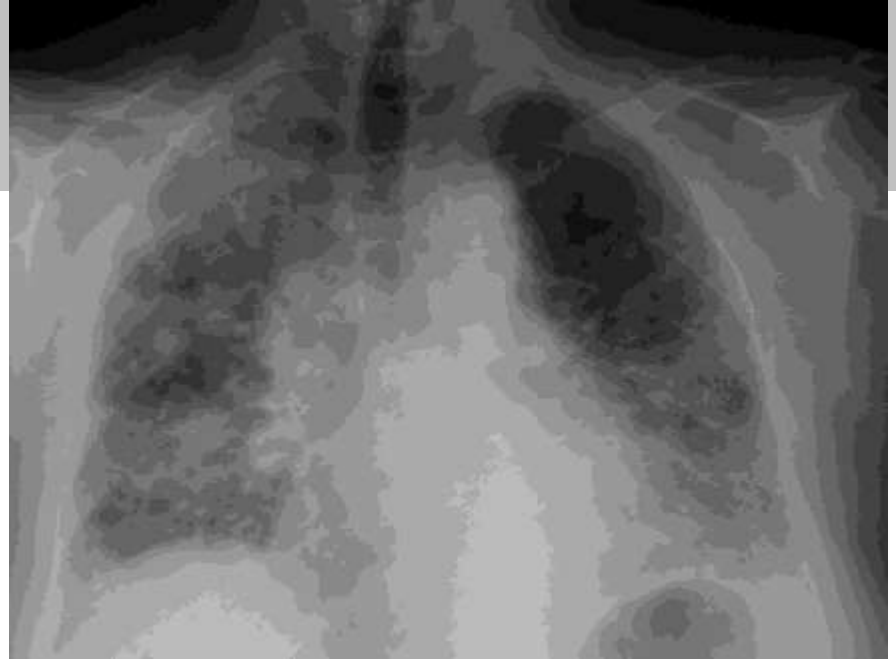


- Causal drugs: Amio, chemo agents (bleo, cyclophosphamide), ImTOR, nitrofurantoin radiation therapy, rituximab
- BOOP *sine* pathology
- Withdrawal +/- empiric CST



- AFOP
  - Amio
  - Statins
  - FOLFOX



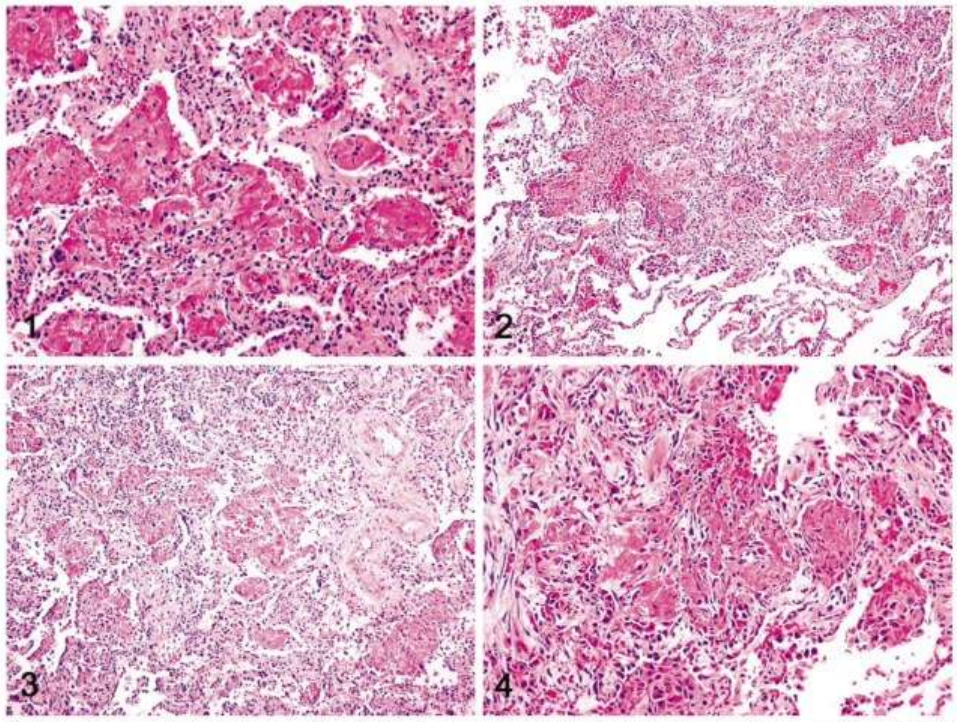
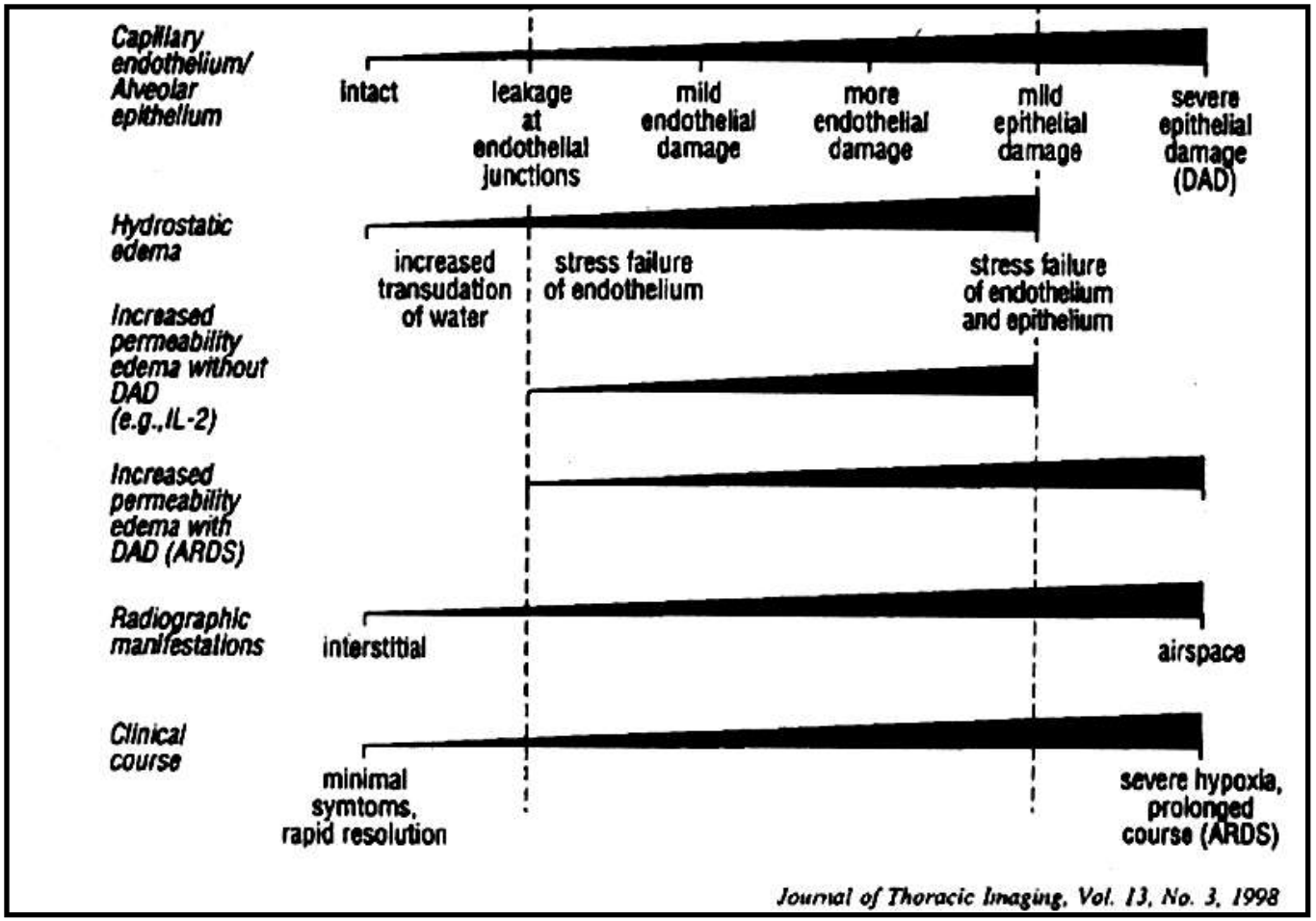
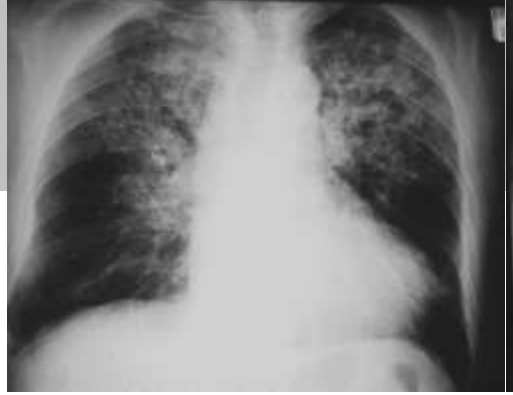
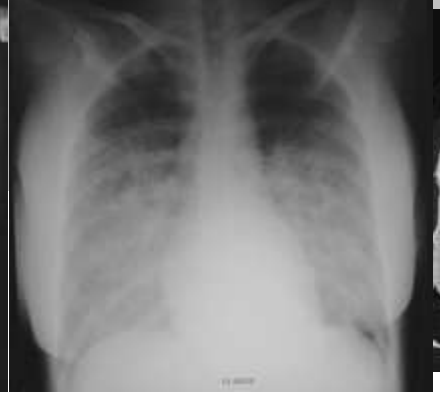
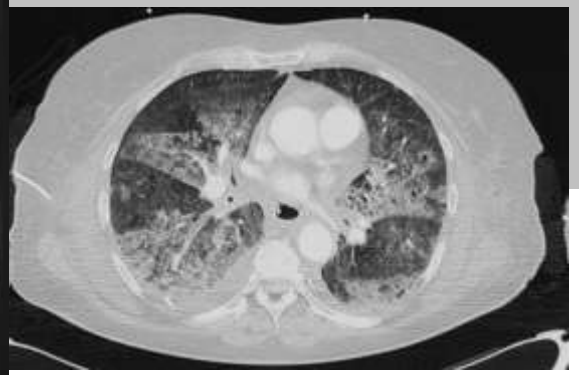
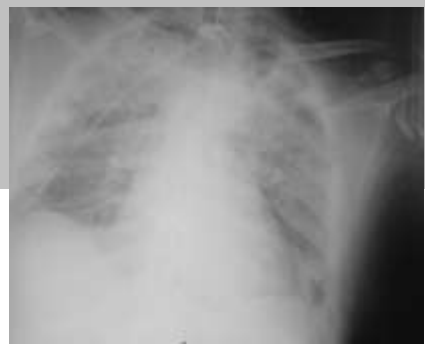
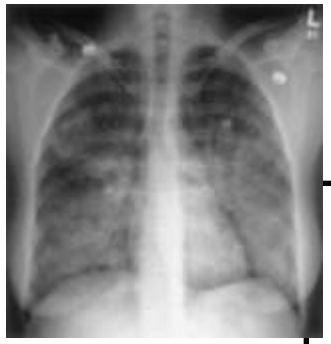
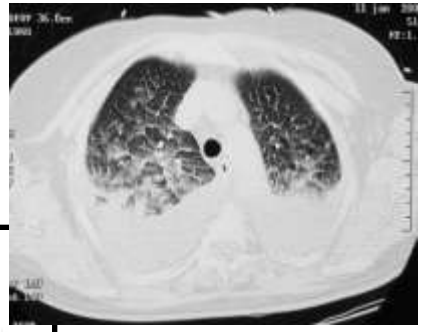


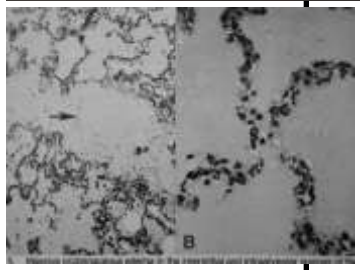
Figure 1. *Intra-alveolar fibrin in the form of "fibrin balls" without formation of hyaline membranes (hematoxylin-eosin, original magnification ×160).*

- Transient pulm. infiltrates <-> NCPE/DAD complex

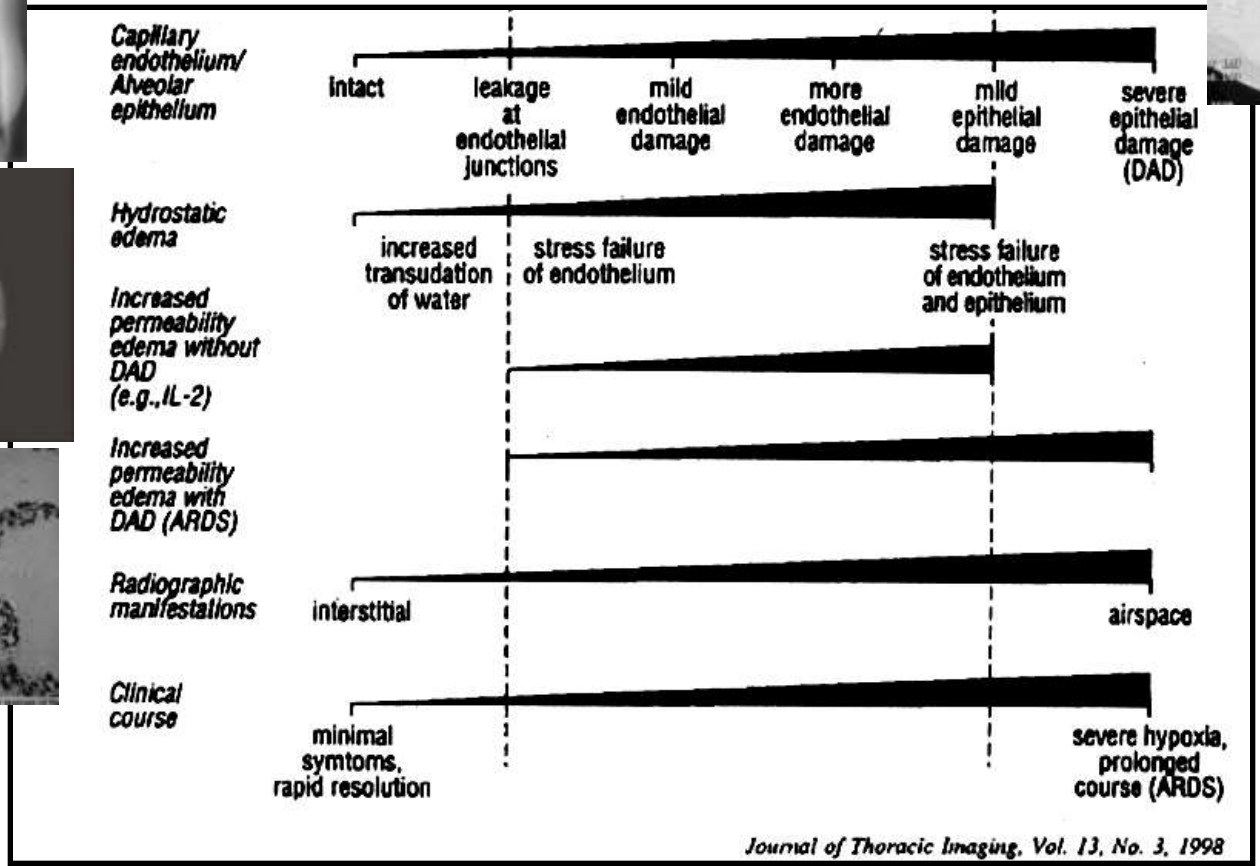
TPI NCPE DAD ARDS



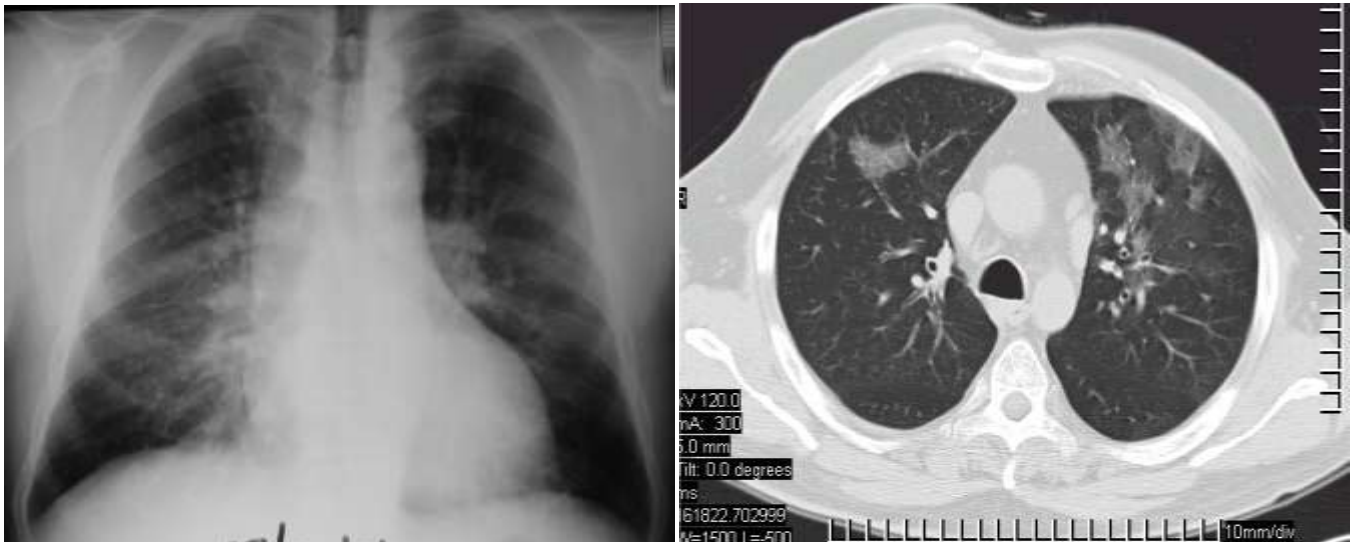


TPI NCPE DAD ARDS



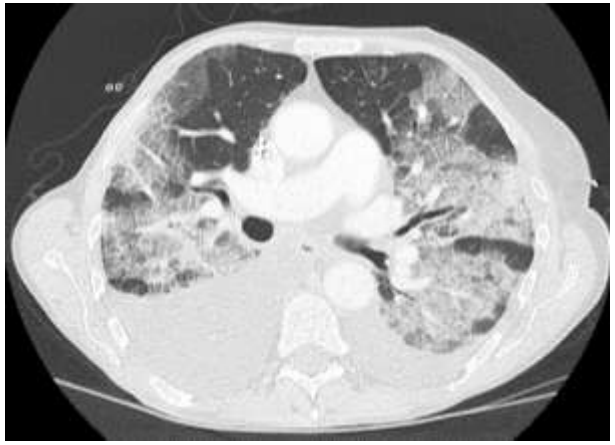
Journal of Thoracic Imaging, Vol. 13, No. 3, 1998

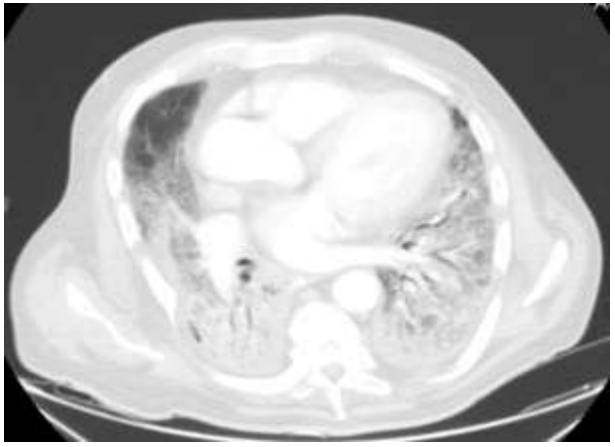
- **Transient pulmonary infiltrates**
  - Gemcitabine, docetaxel/paclitaxel, GM-CSF
  - Most mild and unreported
  - Pathology unknown (?PE-?DAD)
  - Resolve > drug withdrawal ± CST
  - Rechallenge -> risk of more severe episode

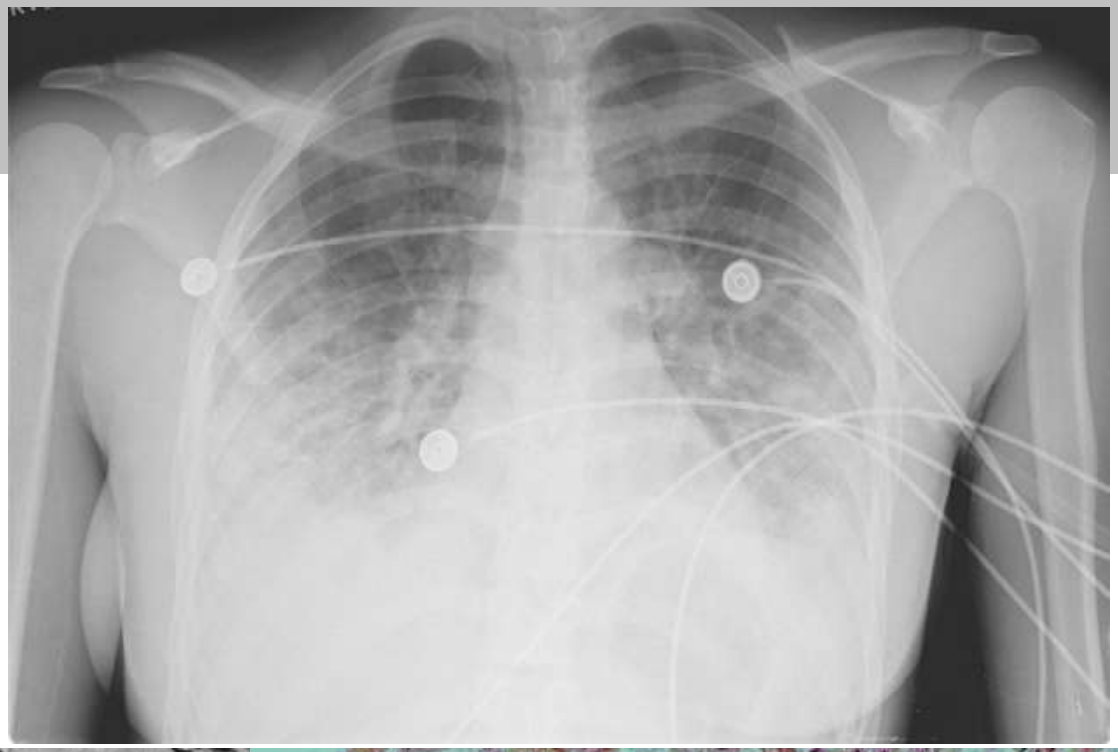


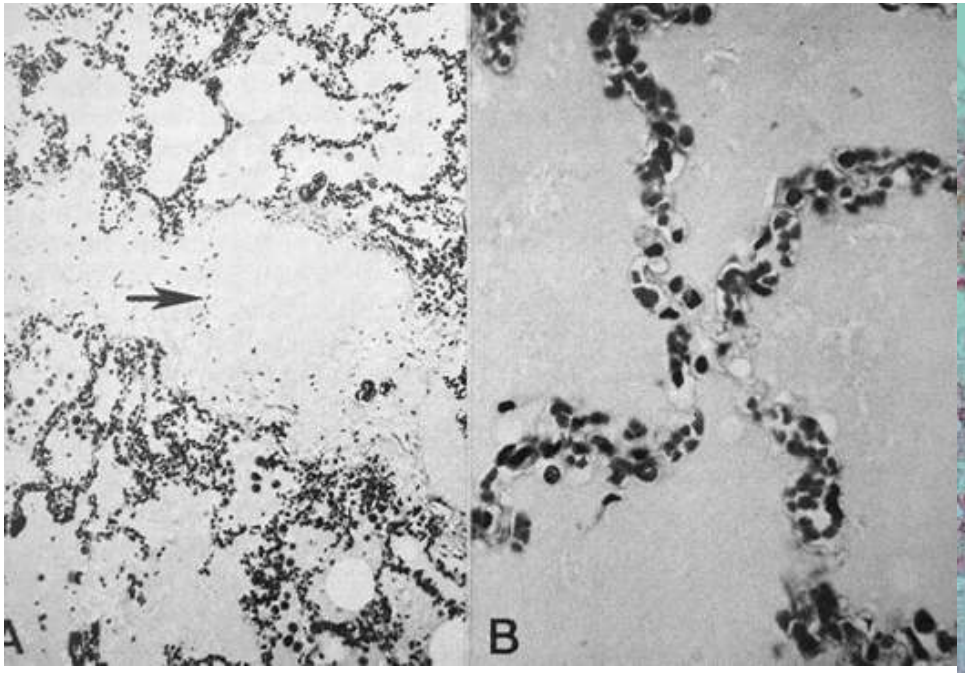
- NCPE
  - Blood transfusion, docetaxel, gemcitabine, mitomycin, vinblastine
- DAD
  - Blood transfusion Chemo (Bleo, Cyclophosphamide, Erlotinib Fluorouracil Gefitinib Gemcitabine Mitomycin C Nitrosoureas) IM-TOR...

- **NCPE - DAD**
  - Cough, tachypnea, low-grade fever, hypoxemia
  - CXR
    - Haze - consolidation
    - Pedicle size / soft tissue swelling (CLS)
  - HRCT
    - Interlobular thickening
    - Confluent alveolar shadowing
    - Diffuse white-out
    - Pleural effusion





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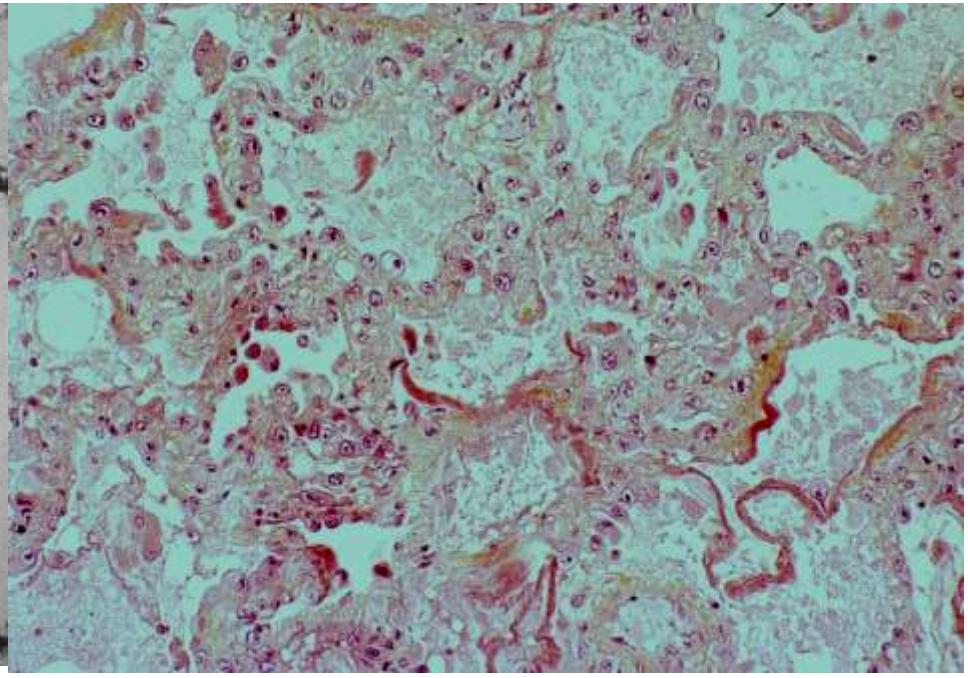


- NCPE
  - Closely follows drug administration
  - Intralobular thickening, pleural effusion
  - Mild-moderate ARDS
  - Resolution 90%
- DAD
  - Time of onset tends to be longer
  - Parenchymal rigidity
  - Resolution 30-40%
- Management
  - Cessation of the implicated agent
  - Search for an alternative explanation
  - CST, supportive care MV

Hemotherapy

- **TRALI**
  - Blood, platelets, IVIG, FFP
  - ARDS within 6hrs of T°
  - Risk factors
    - Plasma-rich product
    - Recent surgery/sepsis (two-hit)
      - 75% immune-mediated anti-HLAI:II HNA3
      - Nonimmune in 15-25%
  - Seperate from TACO
  - Male-only policy
  - Grossly underreported (30%)

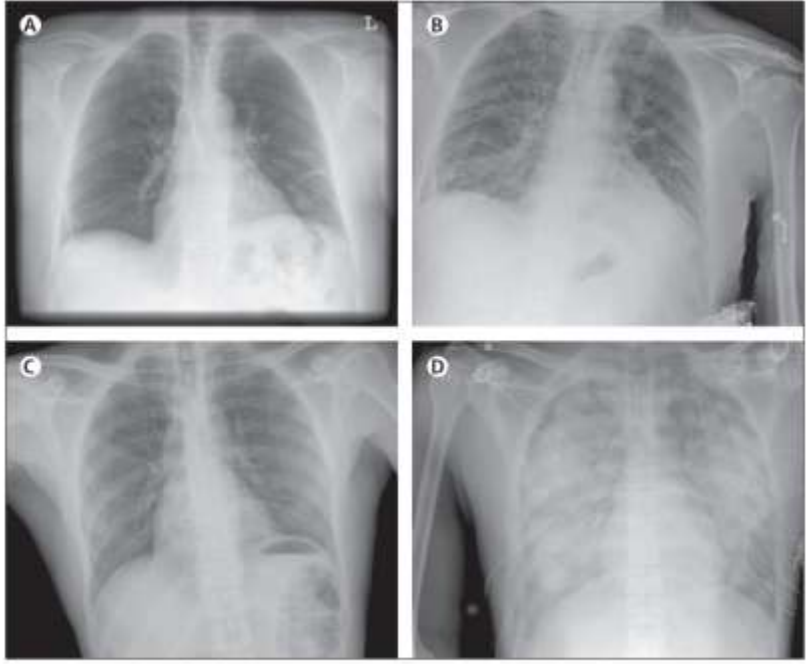
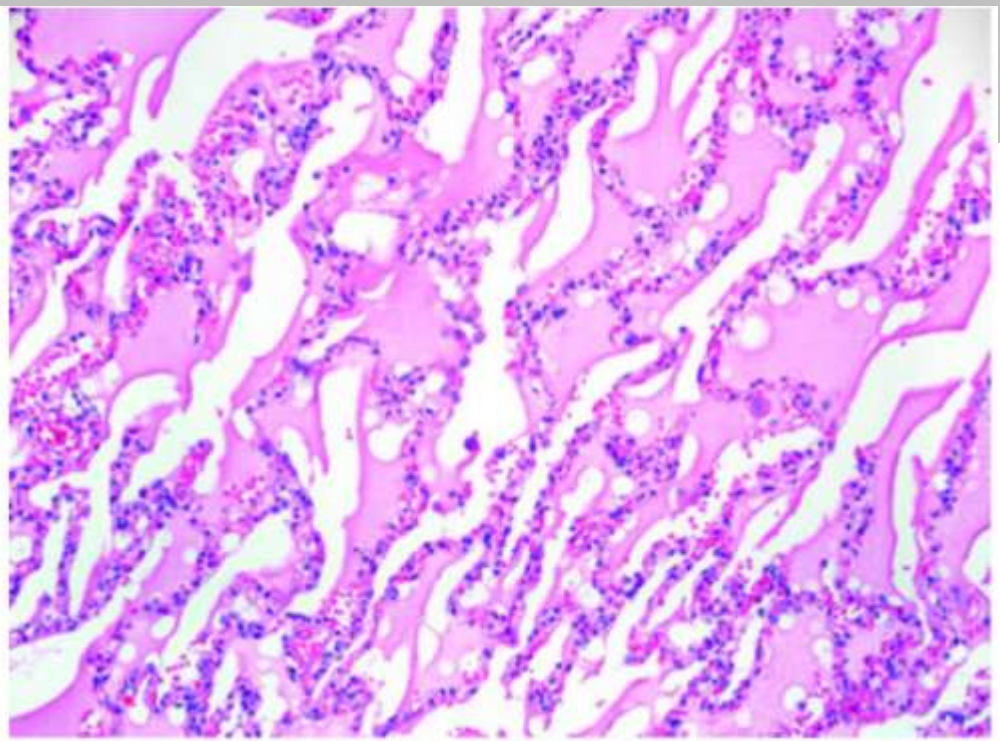
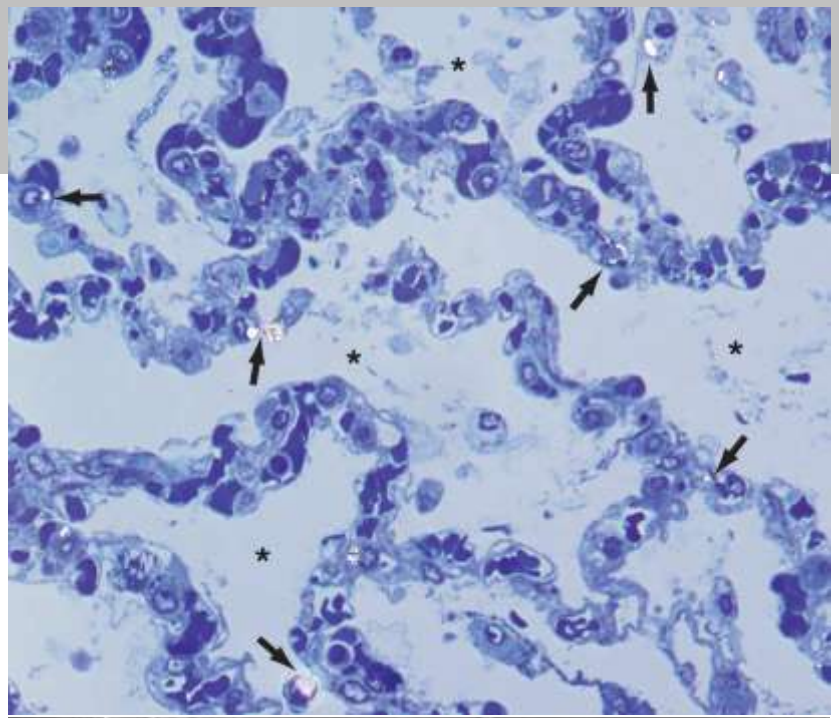


Figure 3: Chest radiographs of patients presenting with transfusion-related acute lung injury (TRALI)





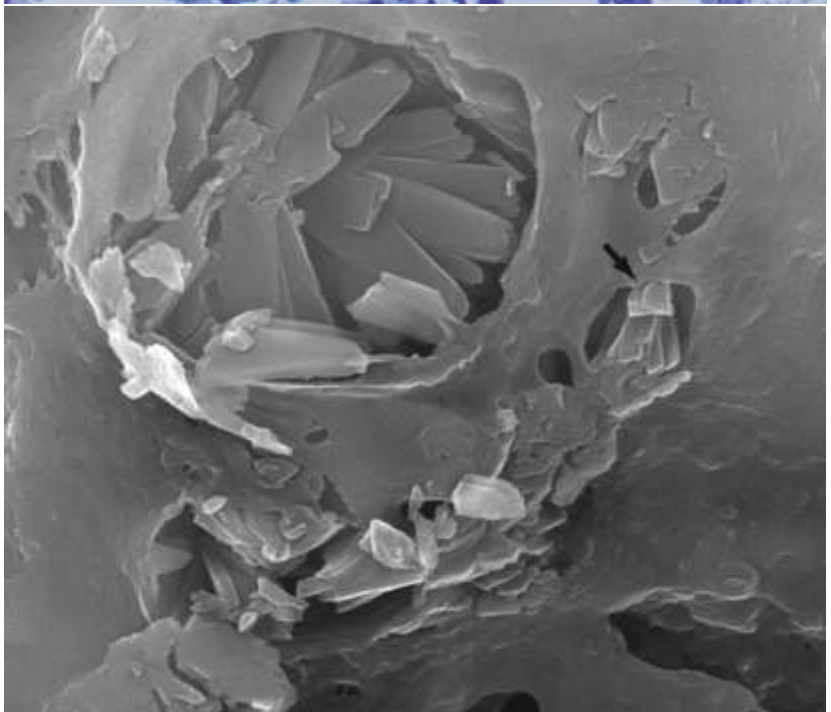


Fig. 1. 100-fold magnification of a hematoxylin and eosin–stained section of parenchymal lung tissue from Patient 1. Patchy pulmonary edema is evident as eosinophilic proteinaceous alveolar material. Although the alveolar capillaries are markedly congested with PMNs and RBCs, there is no WBC accumulation within the alveolar spaces.

Pulmonary Complications of Cocaine Abuse

Chest pain
Airway injury
Pneumothorax
Pneumomediastinum
Pneumopericardium
Pulmonary edema
Exacerbation of asthma
Pulmonary hemorrhage
Bronchiolitis obliterans
Crack lung
Eosinophilic lung disease
Focal airspace disease and atelectasis
Pneumonia
Emphysema
Pulmonary hypertension
Pulmonary infarction
Enlarged lymph nodes

Abused drugs

- **Heroin**
- **Methamphetamine**
  - Pulmonary edema
  - Alveolar hemorrhage
  - Ventilatory depression
  - Vasculopathy & PHT
  - Coronary vasospasm
  - Myocardial infarction
- **Propofol**

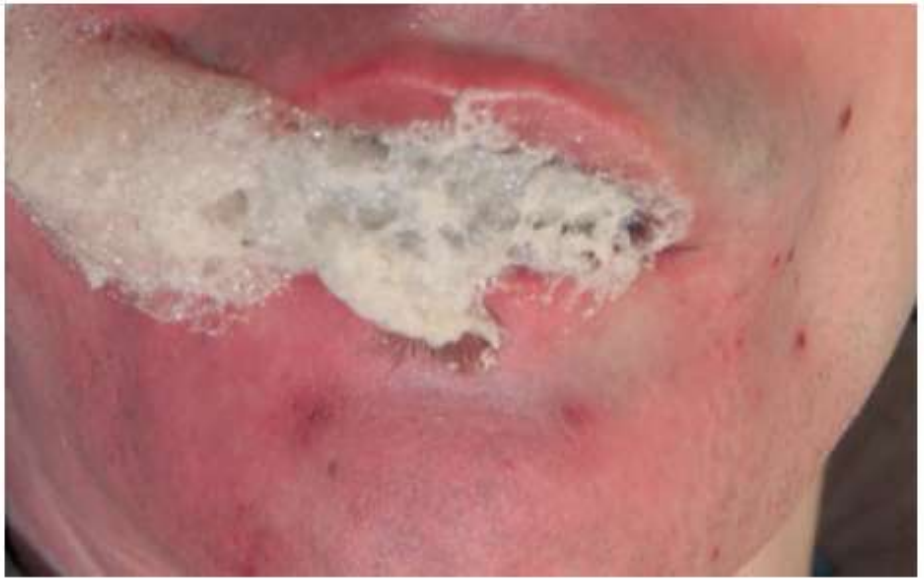


Figure 5. Mushroom plume from pulmonary oedema. This may be seen in opiate deaths.

- Additives, incense, adulterants, cutting agents

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. 5 **a** and **b** Spice compounds submitted by the patient's family for analysis, all of which contained AM-2201. Spice, K2, and similar SC agents are sold in colorful, deceptively packaged 1–3-g mixtures containing dried plant products which have been sprayed with one or more synthetic cannabinoids [17]. These products are marketed with deceptive labels such as "herbal incense" or "potpourri" and packets are labeled "not for human consumption"

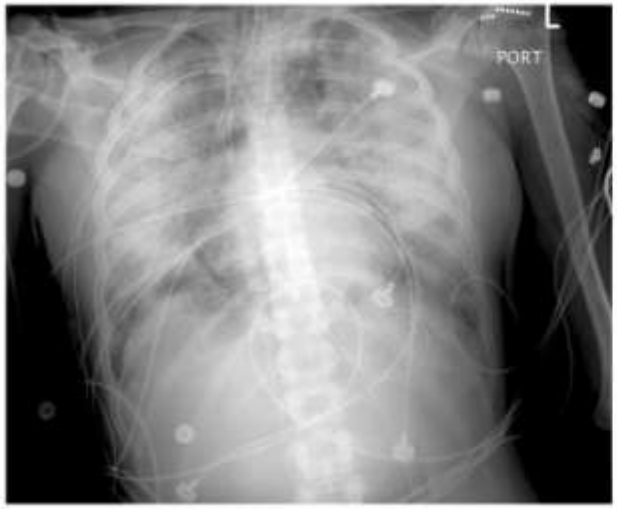


Fig. 1 *Patient 1. Chest radiograph at the time of ECMO cannulation shows diffuse pulmonary infiltrates bilaterally.*

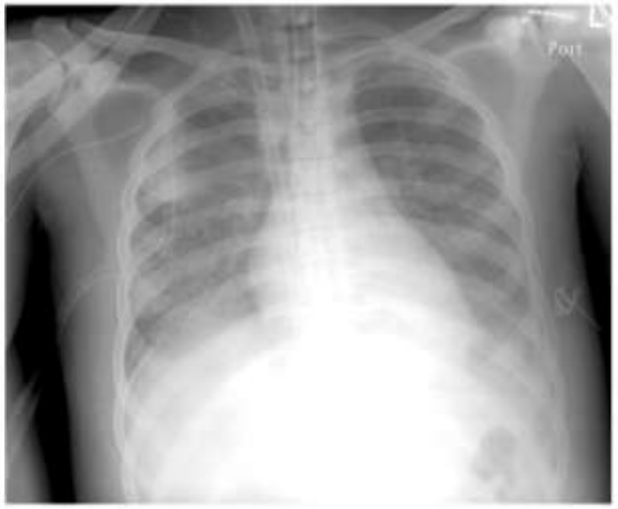
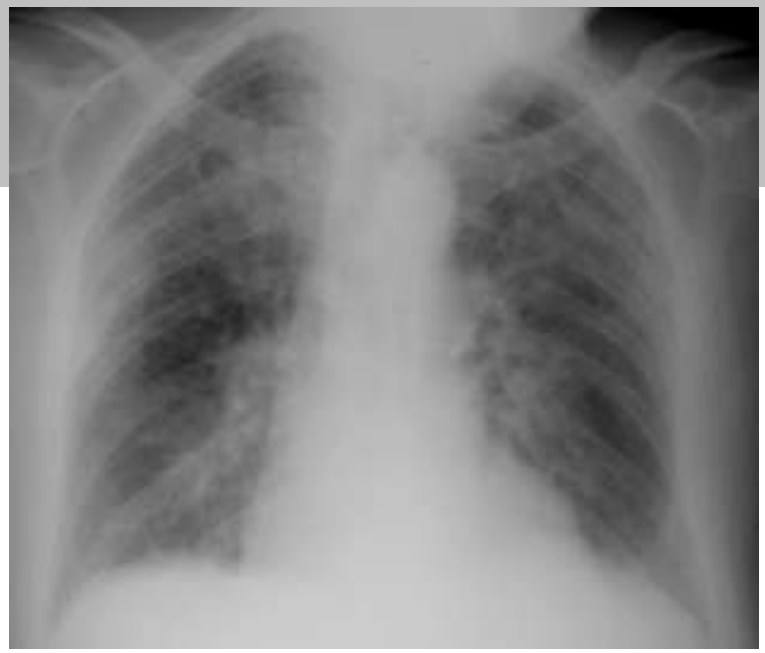
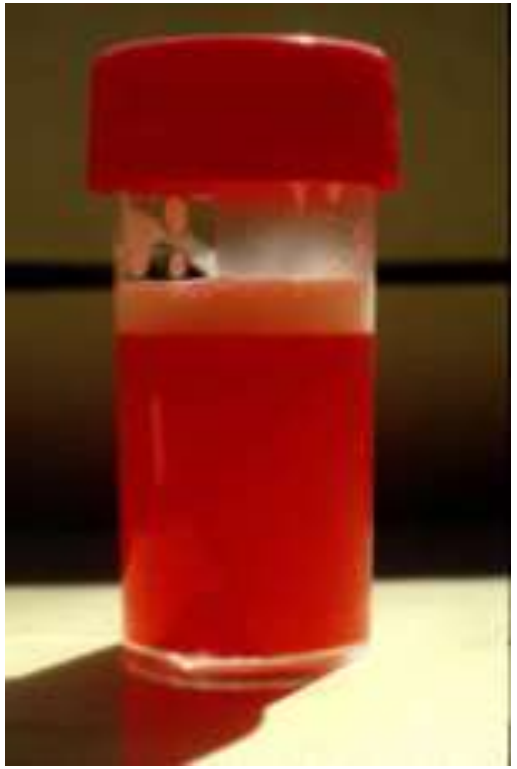


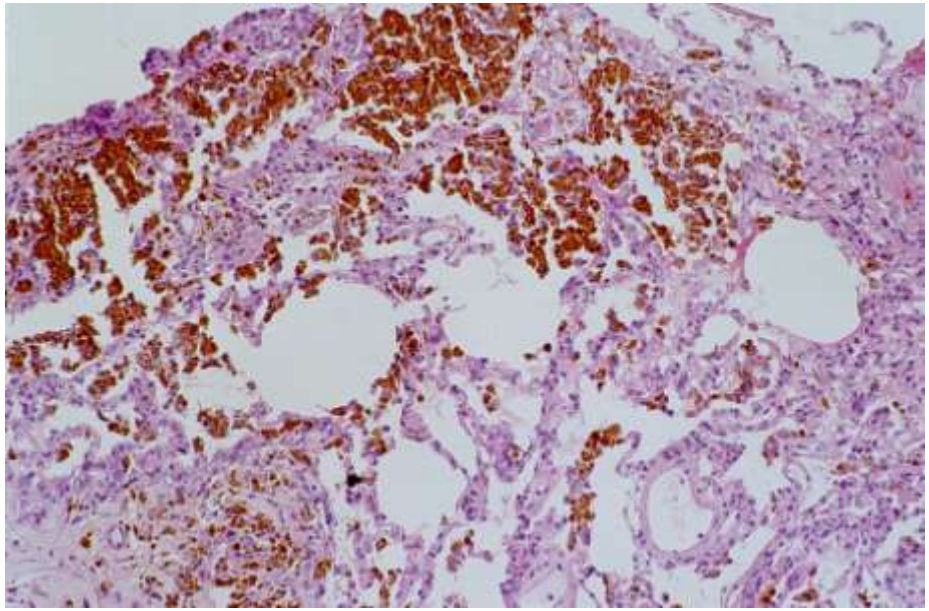
Fig. 2 *Patient 2. Chest radiograph at the time of ECMO cannulation shows diffuse pulmonary infiltrates bilaterally.*

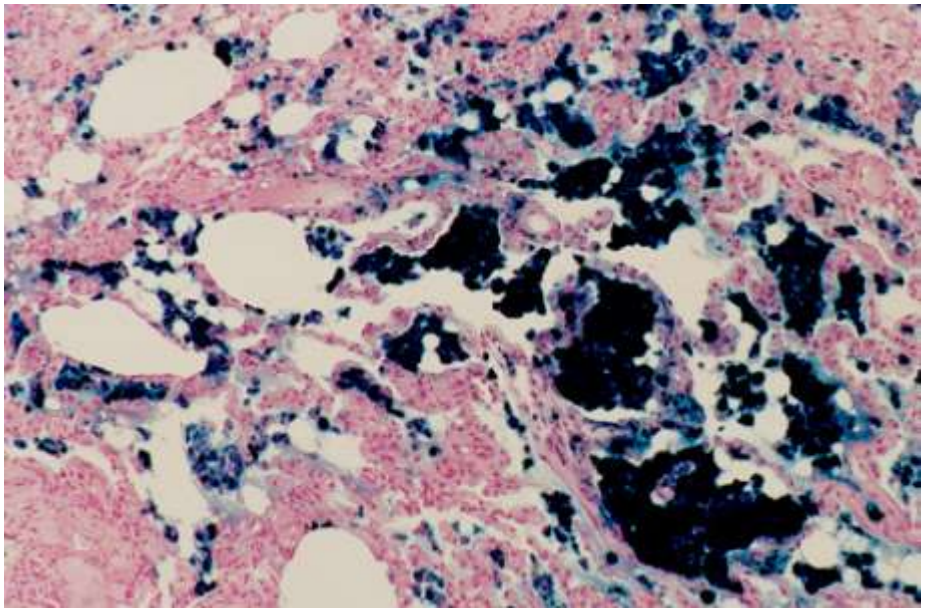
Alveolar hemorrhage

- Causal agents
  - Oral anticoagulants, superwarfarins
  - Antiplatelets
  - Direct anticoagulants
  - Heparin, SK, UK, alteplase
  - mTOR inhibitors (sirolimus)
  - Propythiouracil
  - Cocaine - levamisole
- Can be fatal



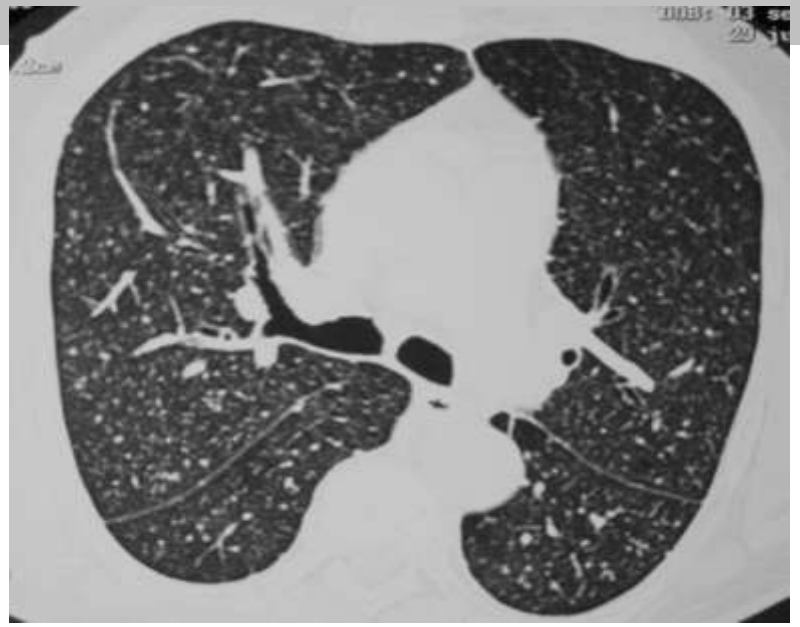






ILD with a granulomatous component

- Causal drugs: BCG, IVDU etanercept, everolimus interferons, methotrexate
- Rule out an infection (TB, PJ)
  - BAL
  - IGRA



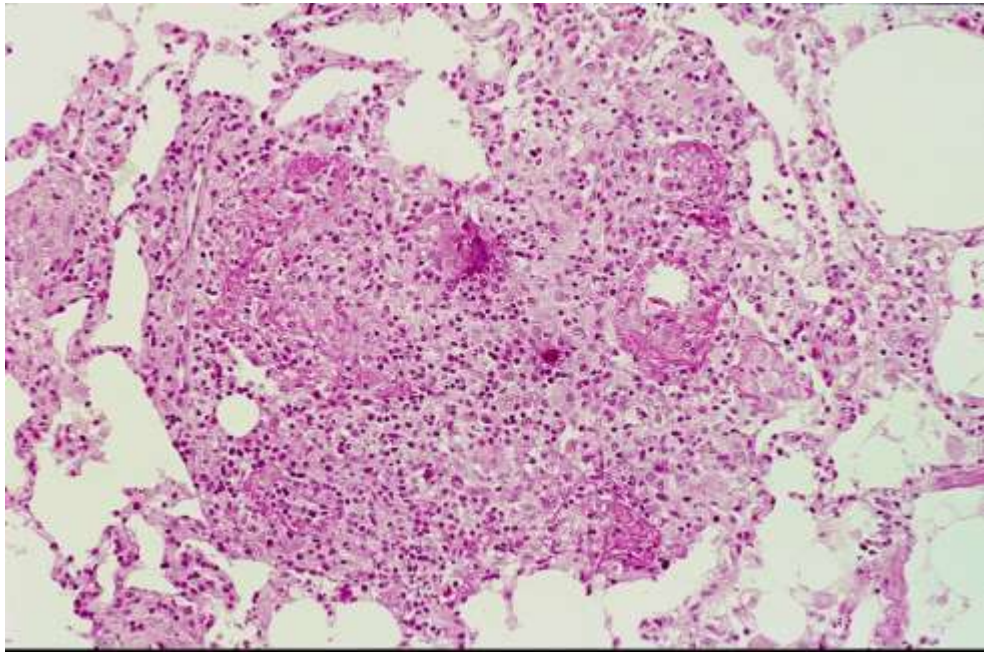


Table 1
Frequently used additives/diluents to adulterate street drugs [22].

Quinine
Mannitol
Lactose
Glucose
Procaine
Caffeine
Inositol
Lidocaine
Starches
Methapyrilene
Sucrose
Acetylprocaine
Dextrose
Scopolamine
Paracetamol
Phenobarbital
Methaqualone

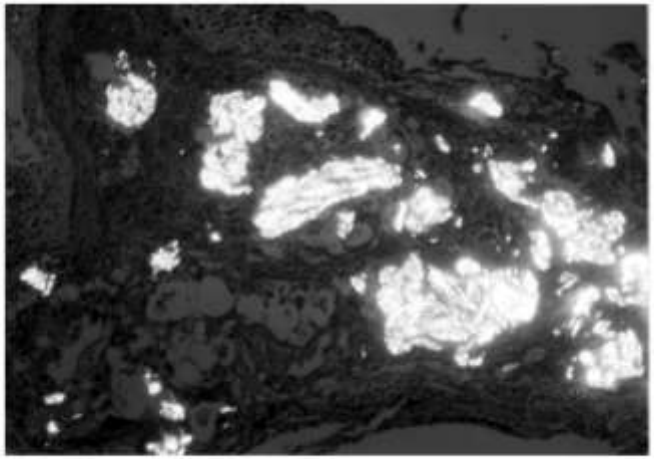


FIG. 3 *The embolic material in the pulmonary arteries shows intense birefringence when examined under polarized light.* ×400.

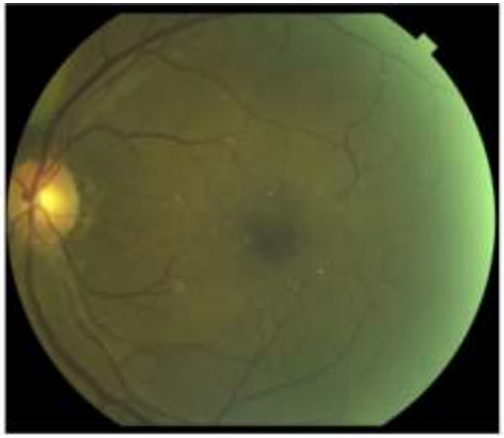
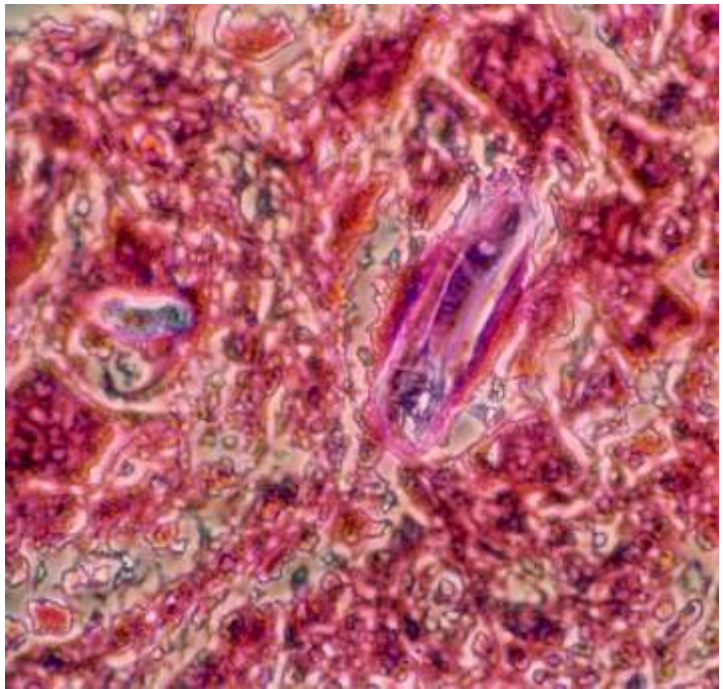
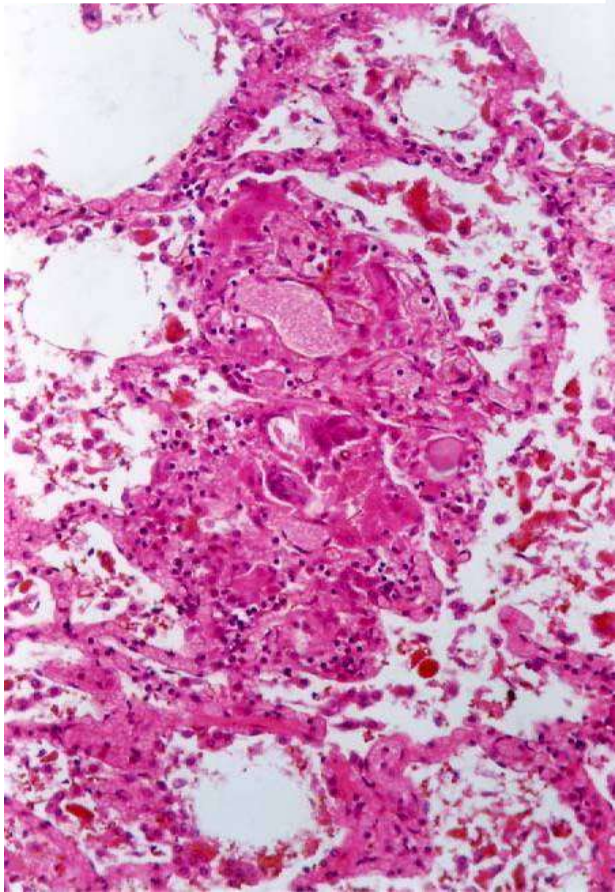


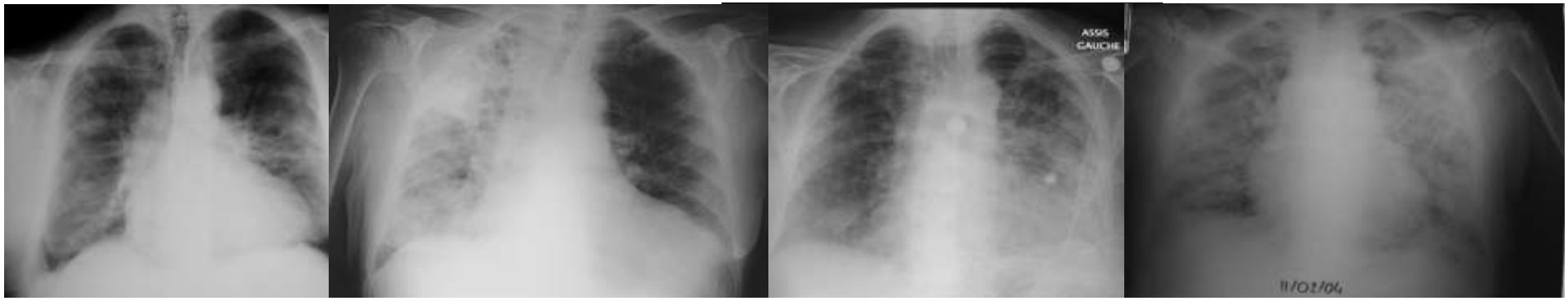
FIGURE 1. Fundoscopic image of the retina.

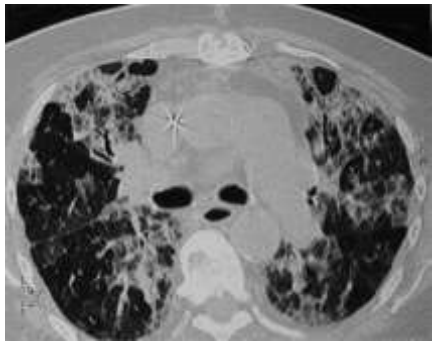


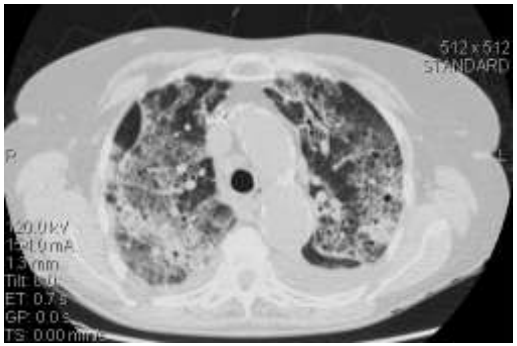


Amiodarone pulmonary toxicity (APT)

- Typical age >60
- 6-12 mo into treatment (150-180 g)
- Insidious onset (weeks-months)
- Dyspnea, cough, moderate fever, pleuritic chest pain
- Multiple possible presentations



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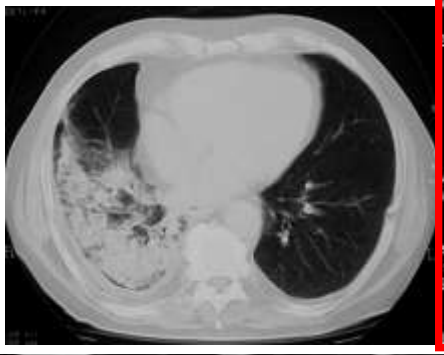

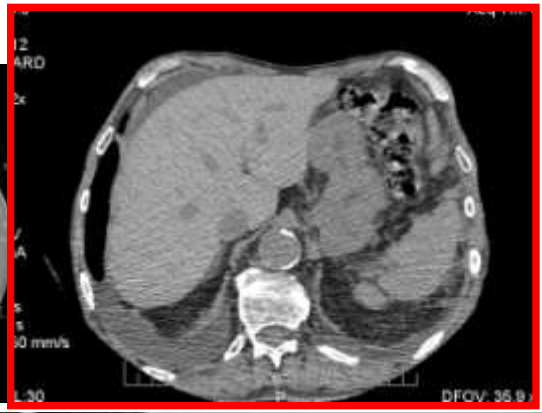
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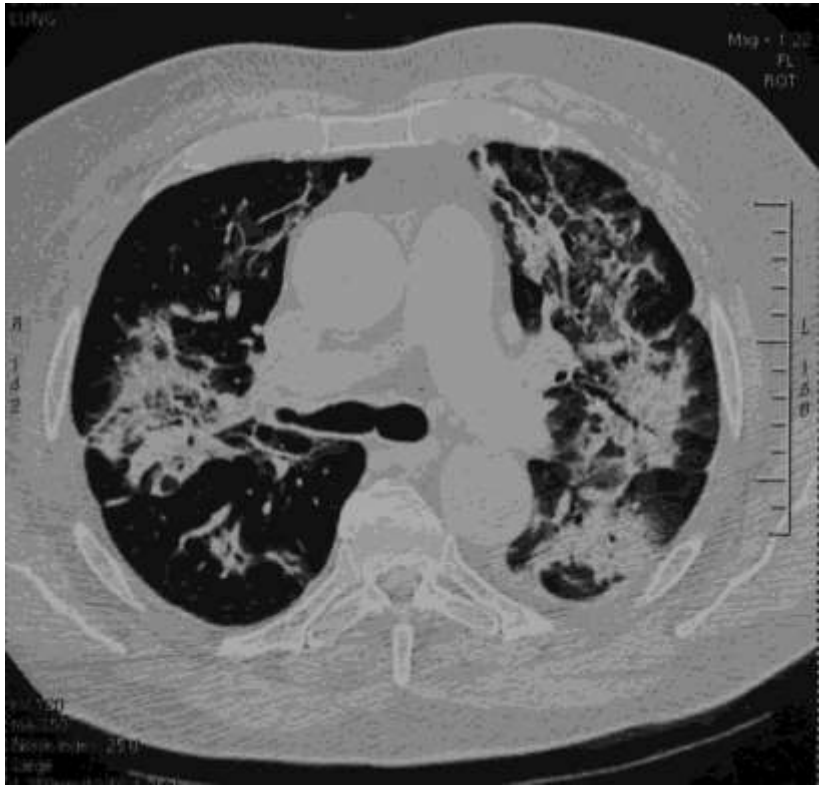

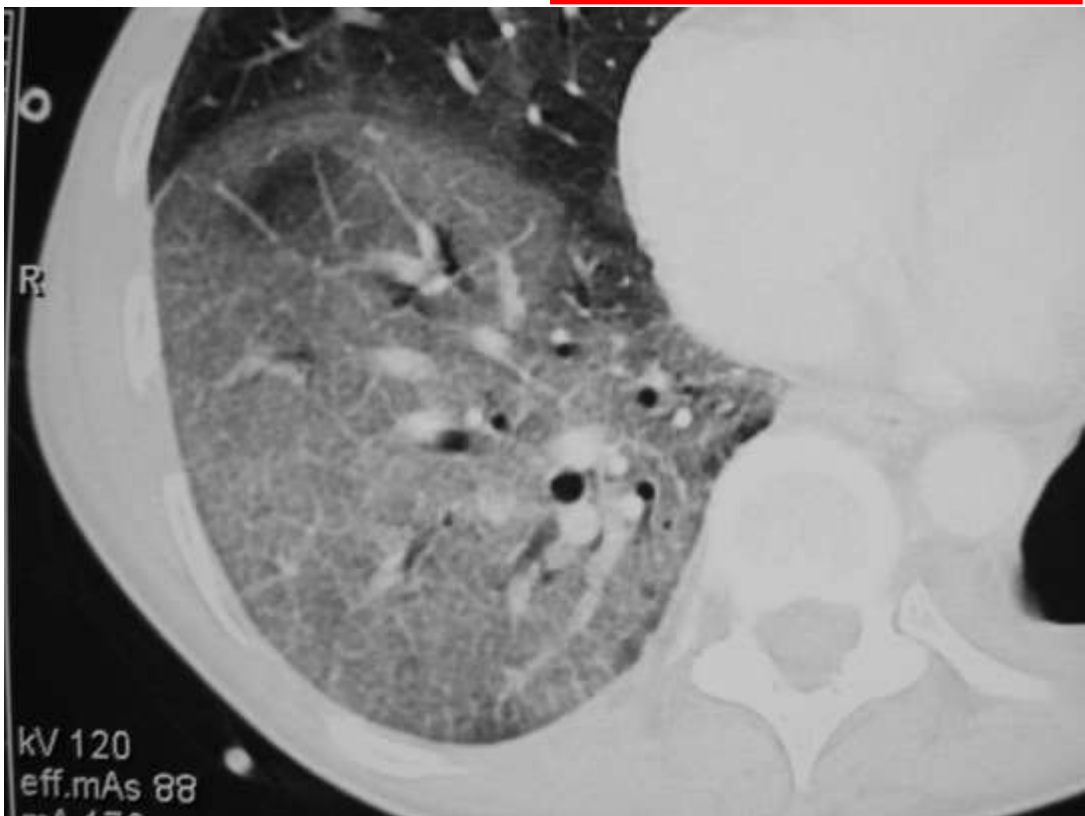
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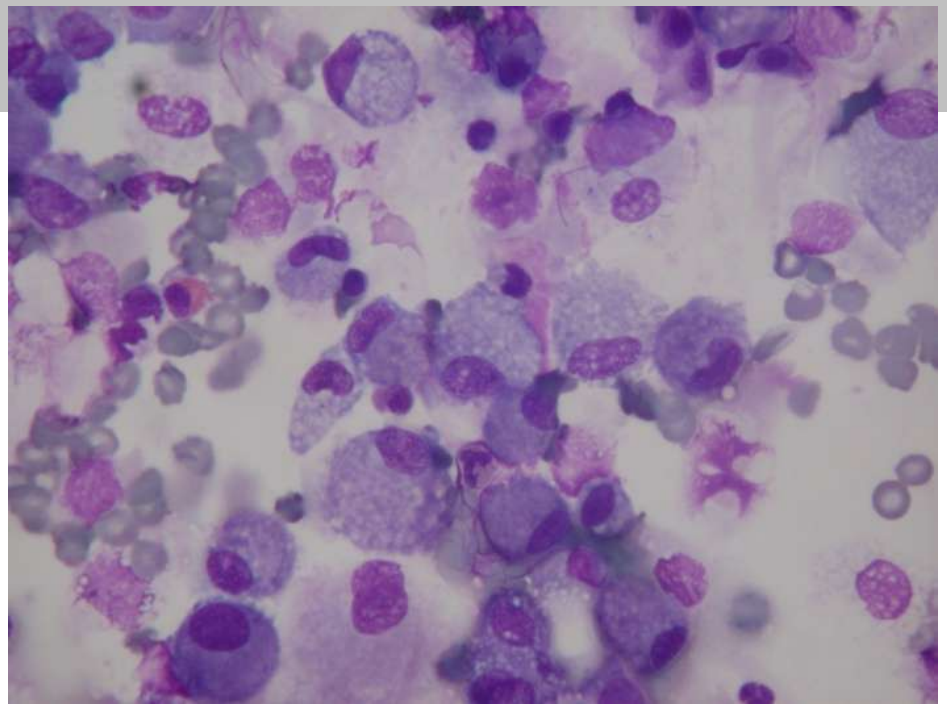
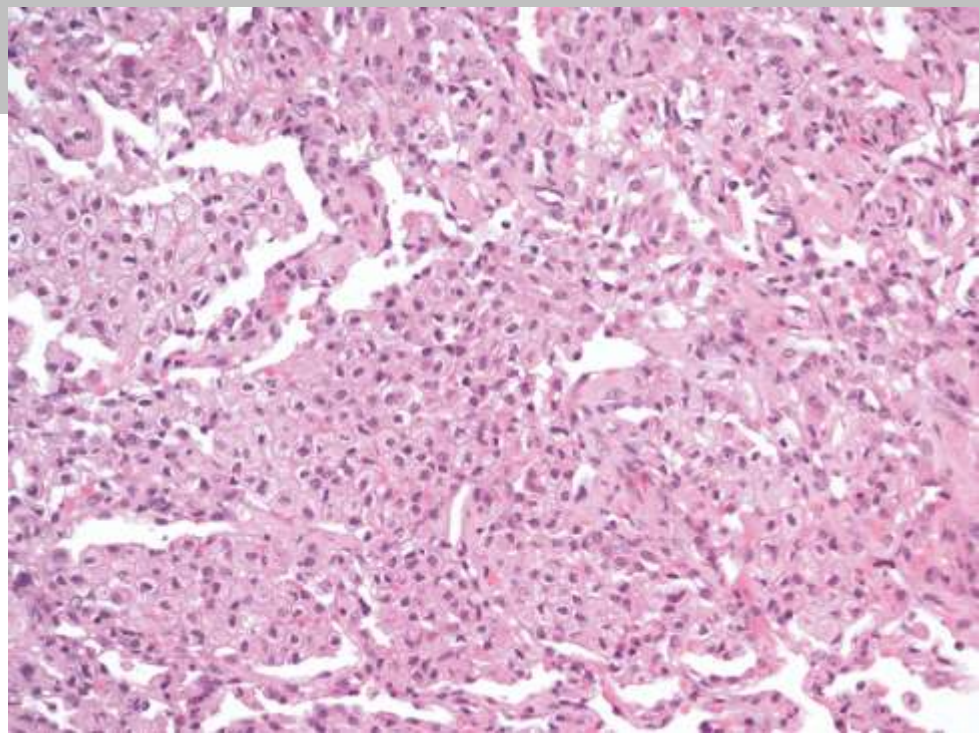
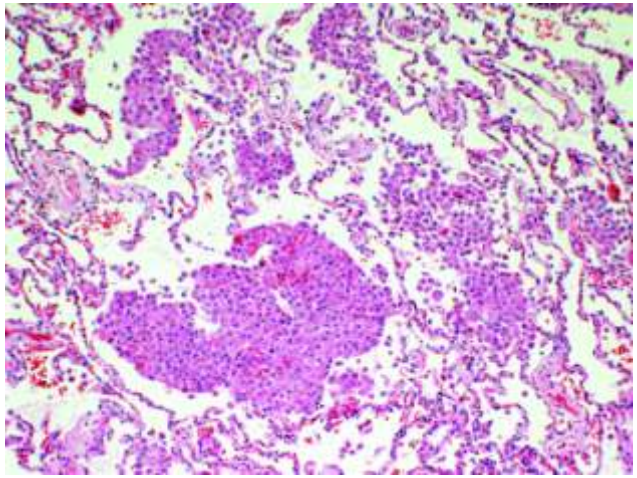
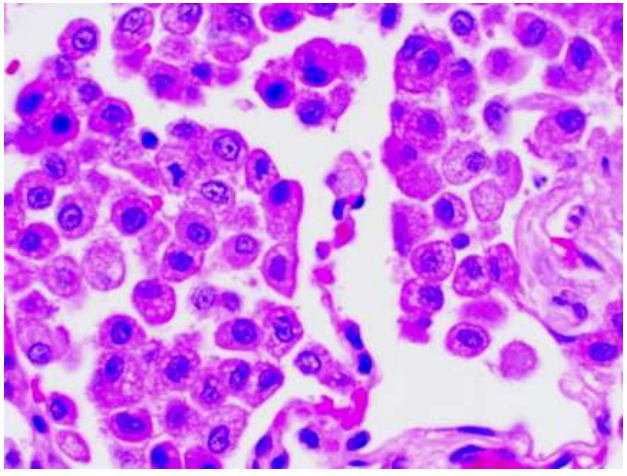
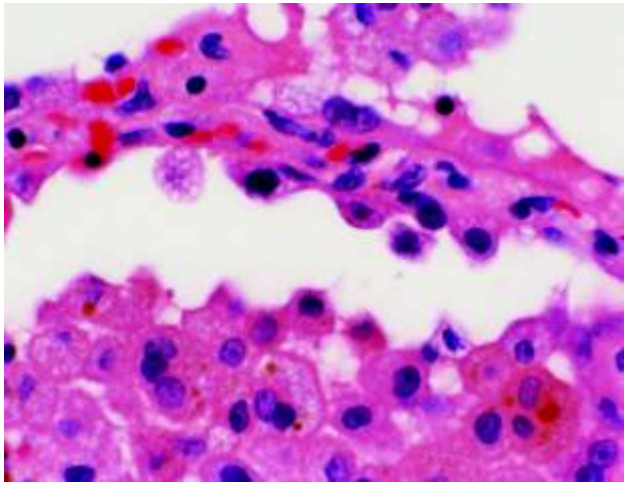




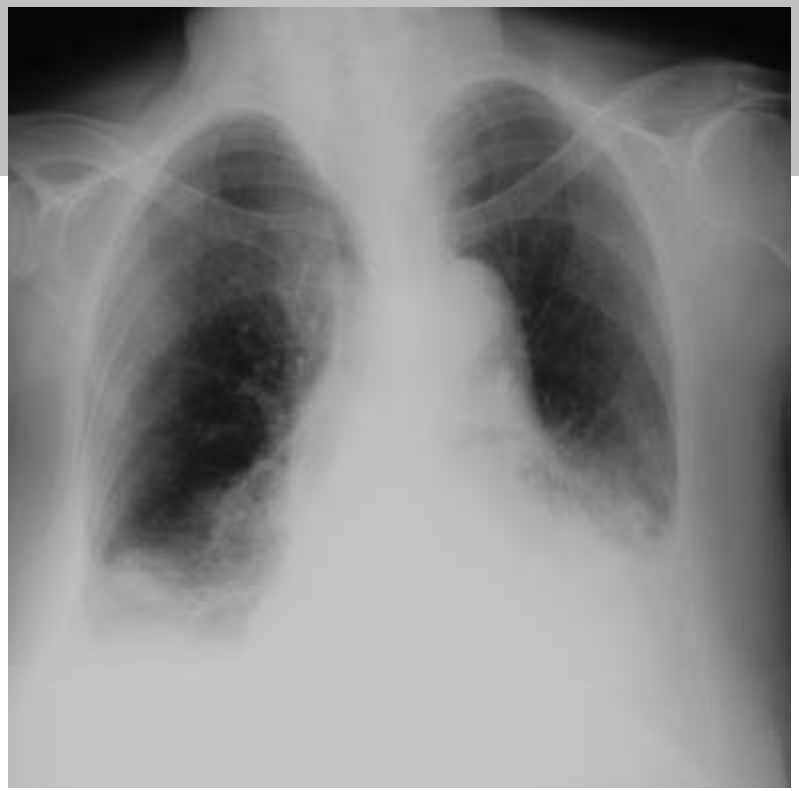


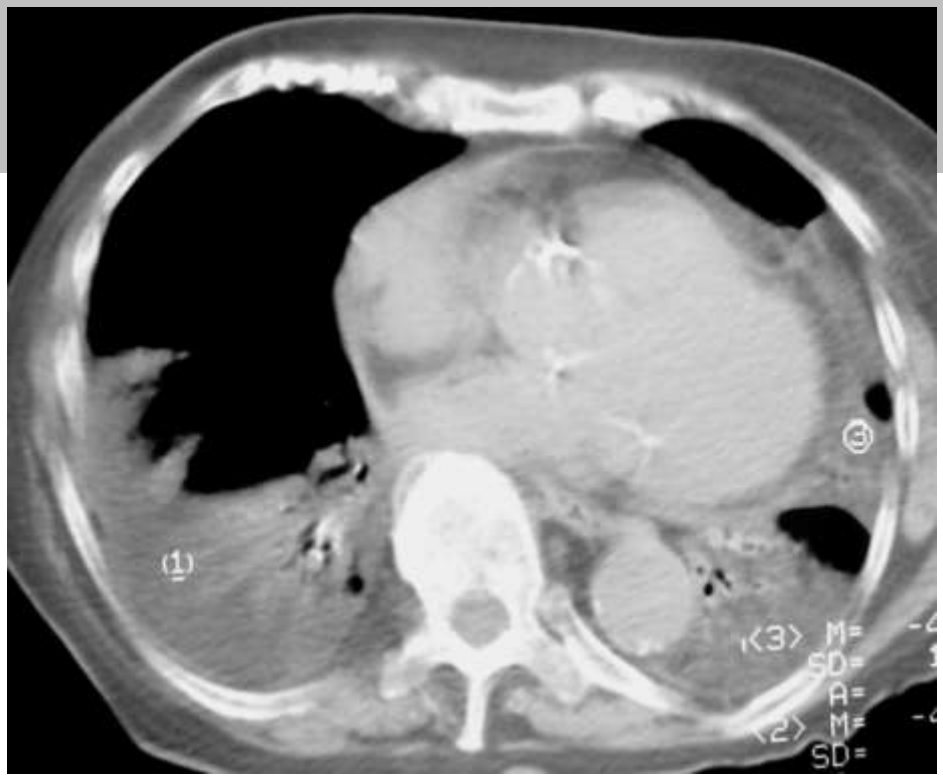




Rare distinctive patterns

- Exogenous lipoid pneumonia
- Fire-eater's lung
- Pleuropulmonary fibroelastosis PPFE
- Lung nodules
- DIP
- Nonthrombotic pulmonary embolism
- PAP-pattern
- Diffuse calcification
- LAMM

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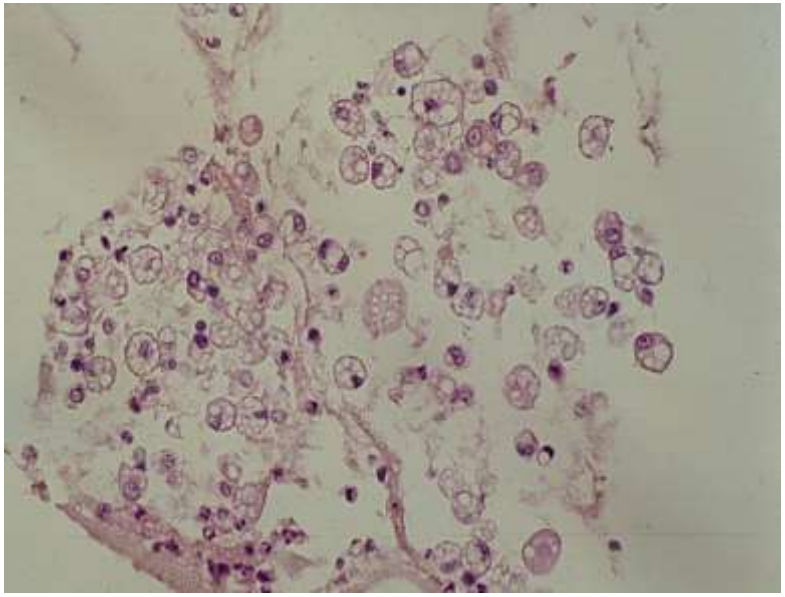
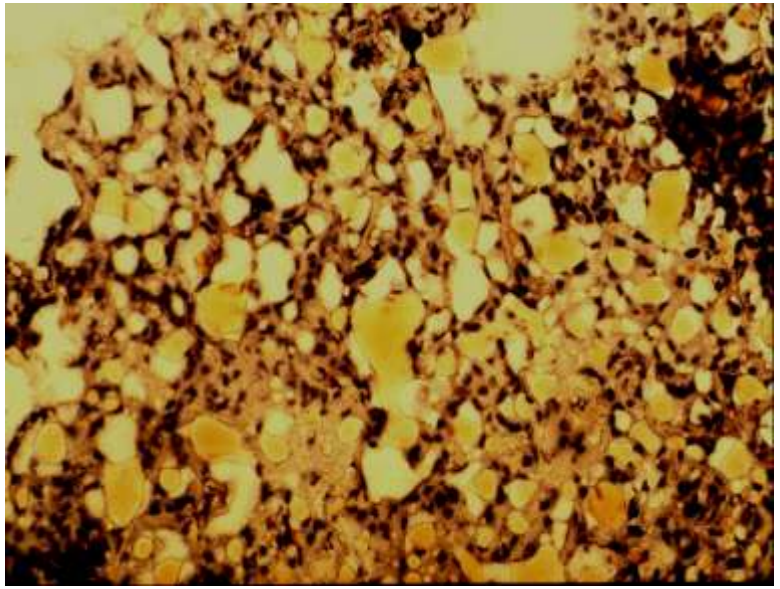
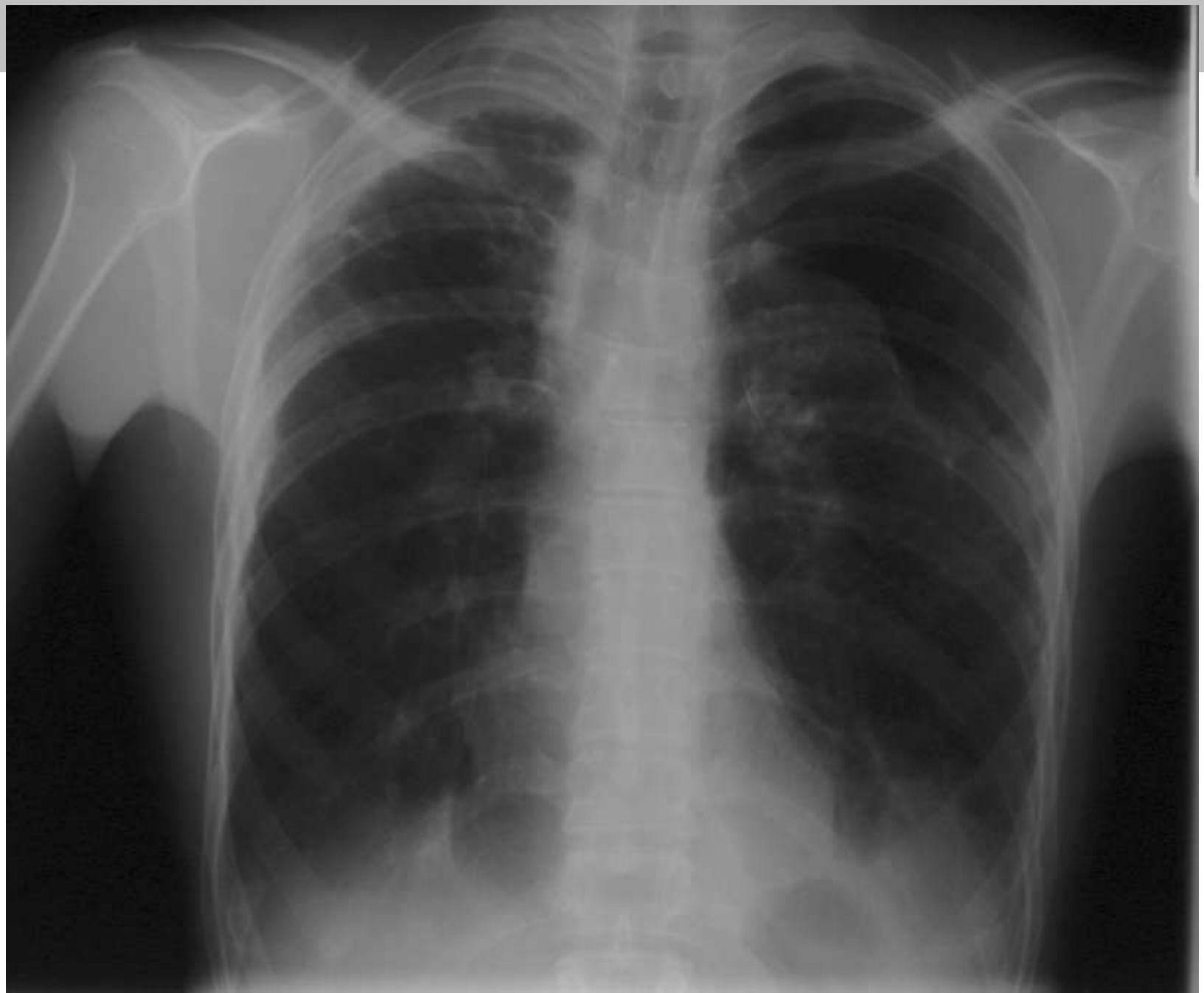
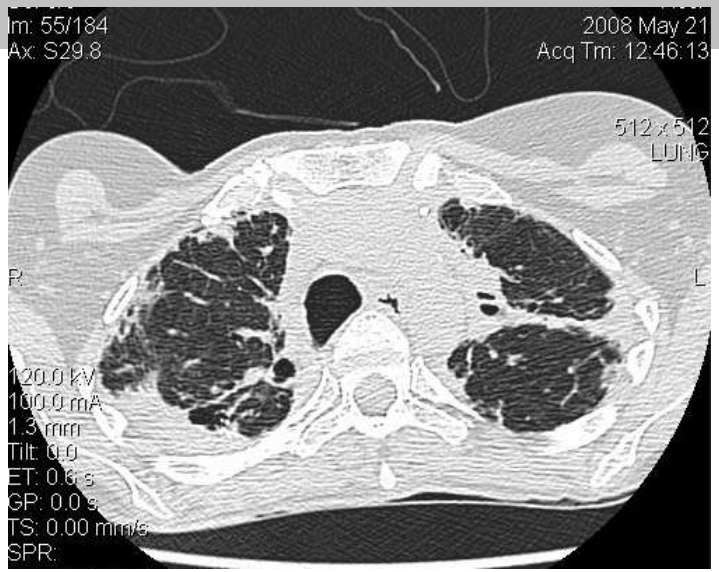
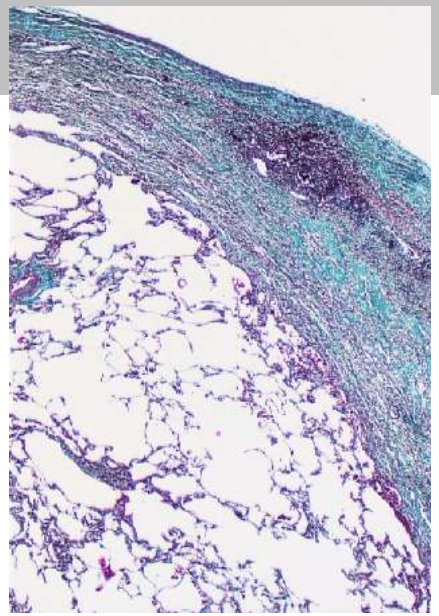


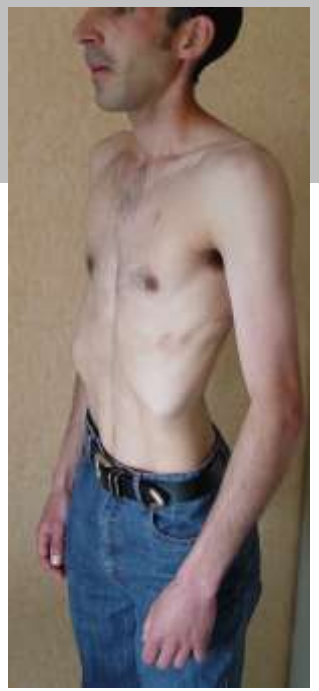




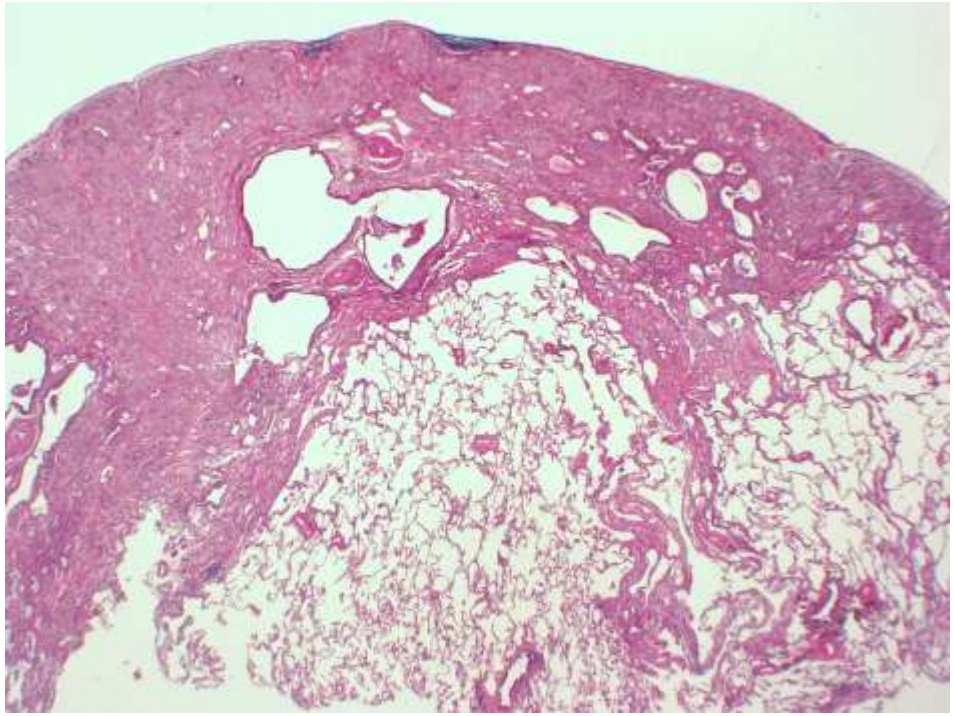
PPFE

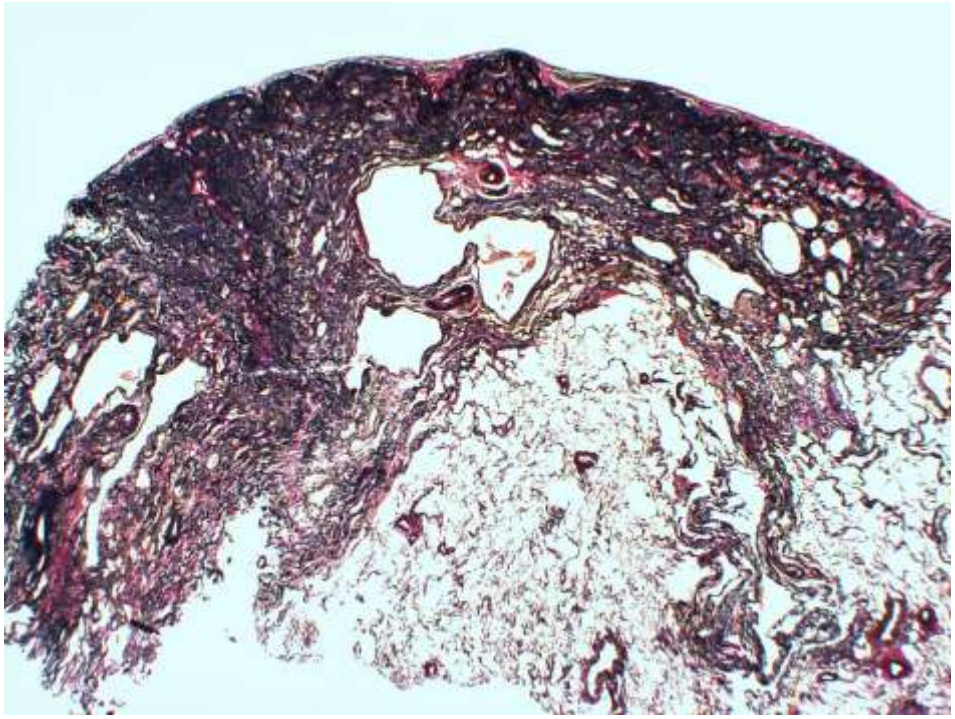




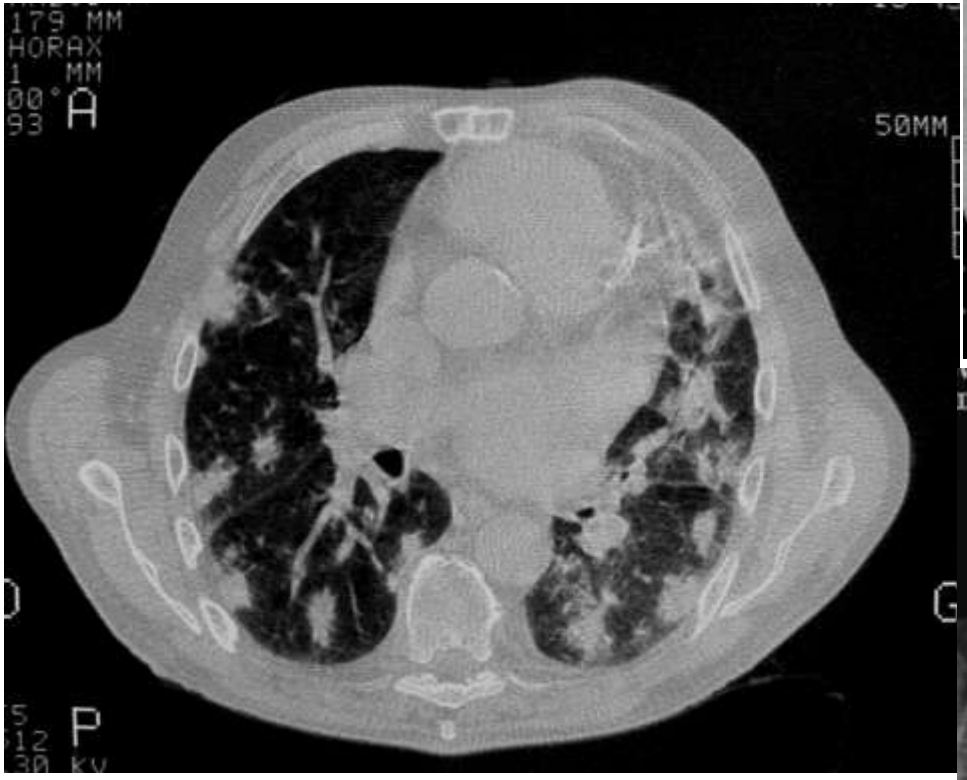


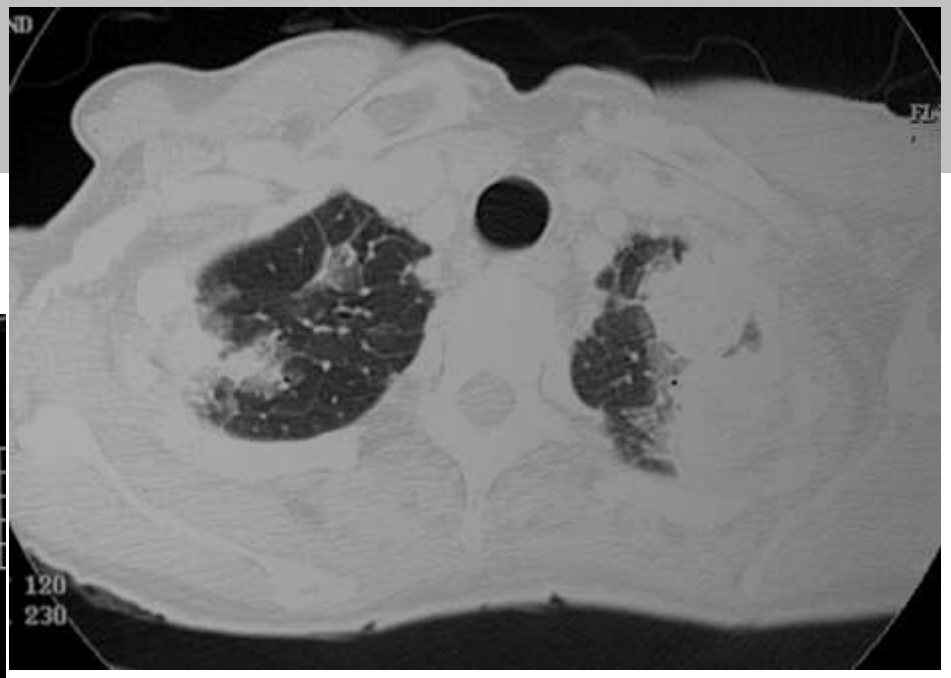
- Dyspnea, chest pain
- Platythorax
- Restrictive lung function defect, often severe
- Distinctive imaging
- Significant Hx: Lung Tx 50%. Exposure to cyclophosphamide 10%

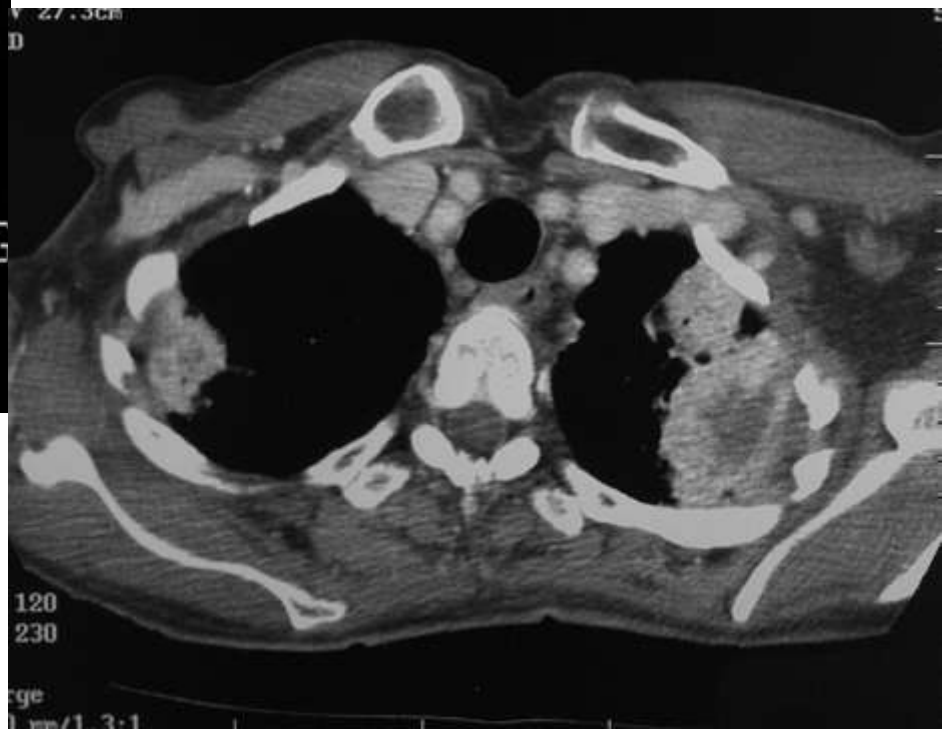


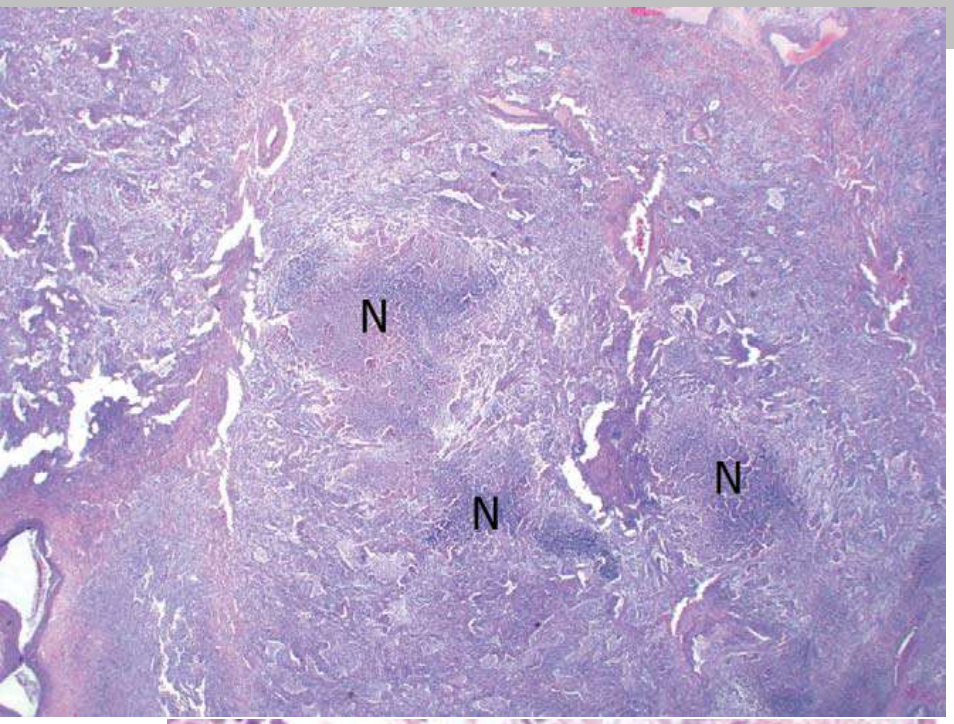


Lung nodules





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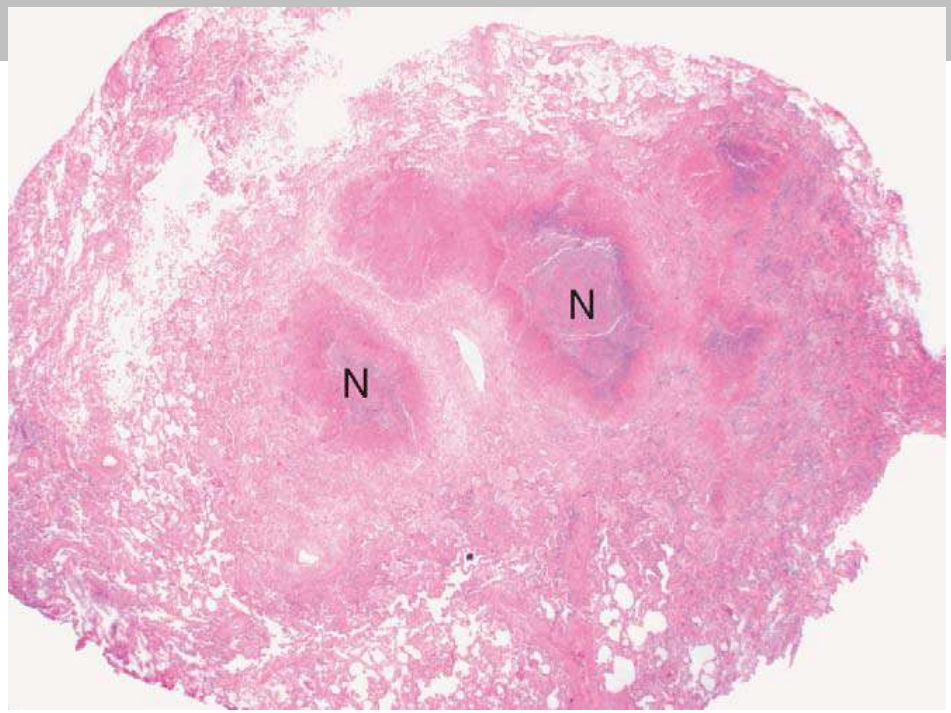
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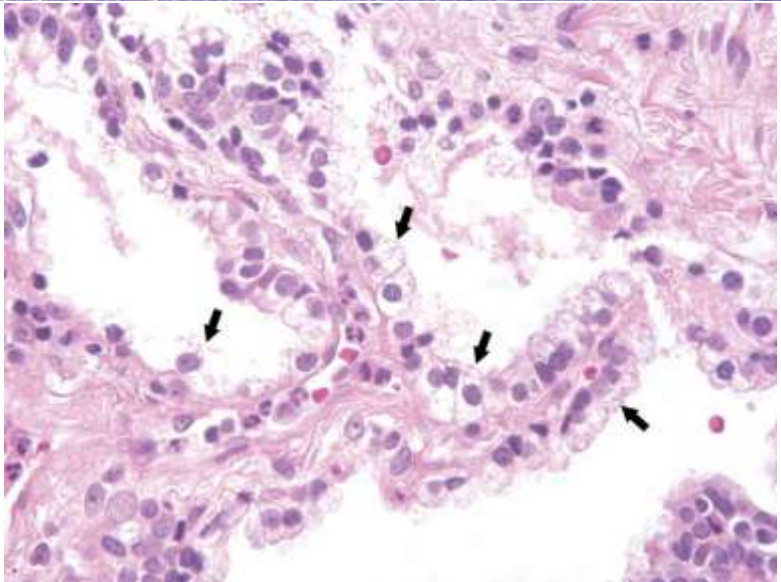
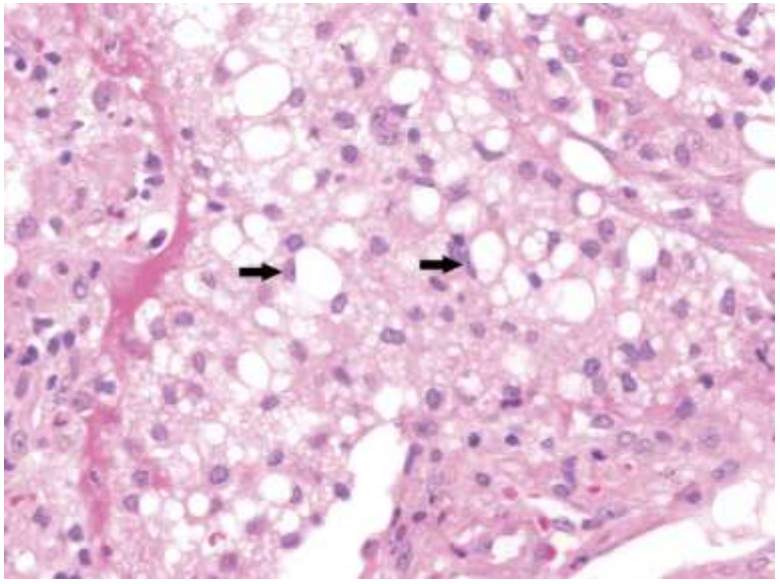
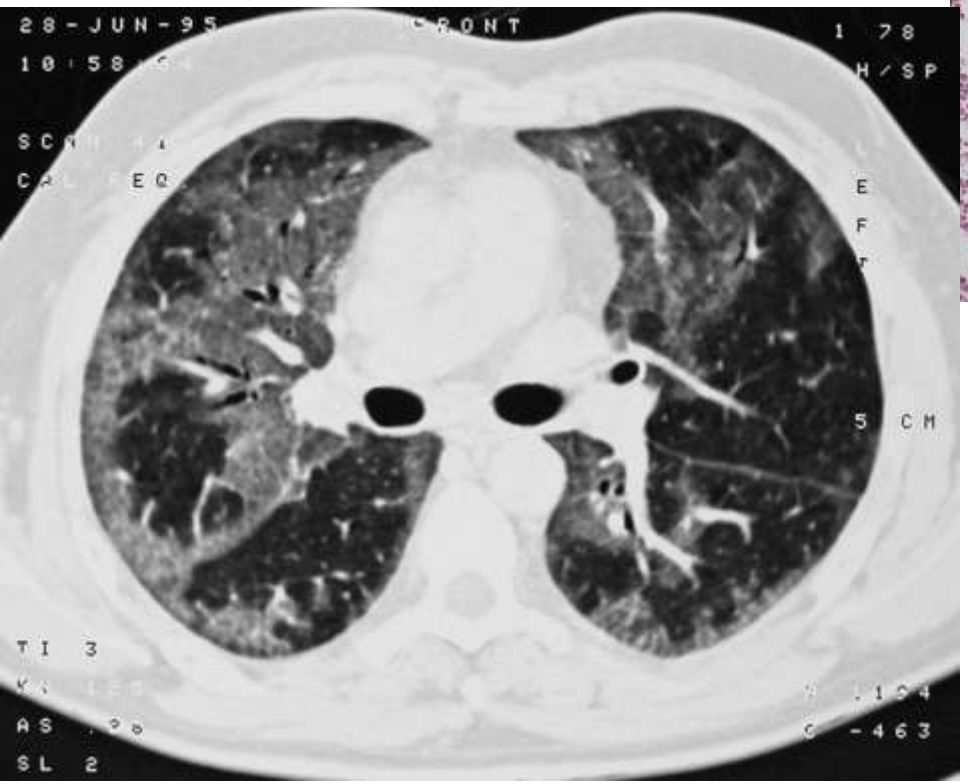
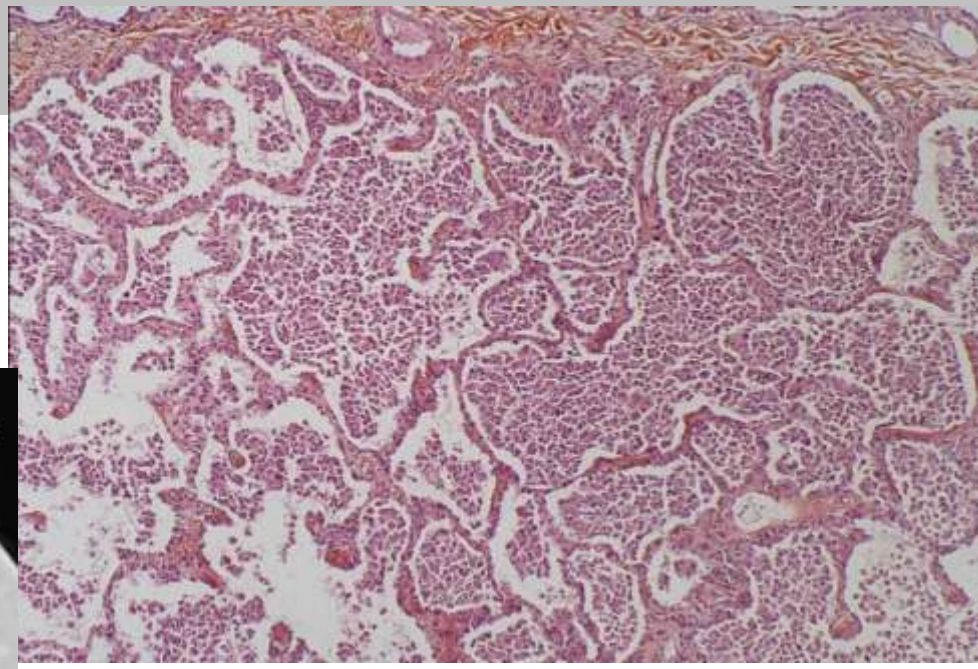


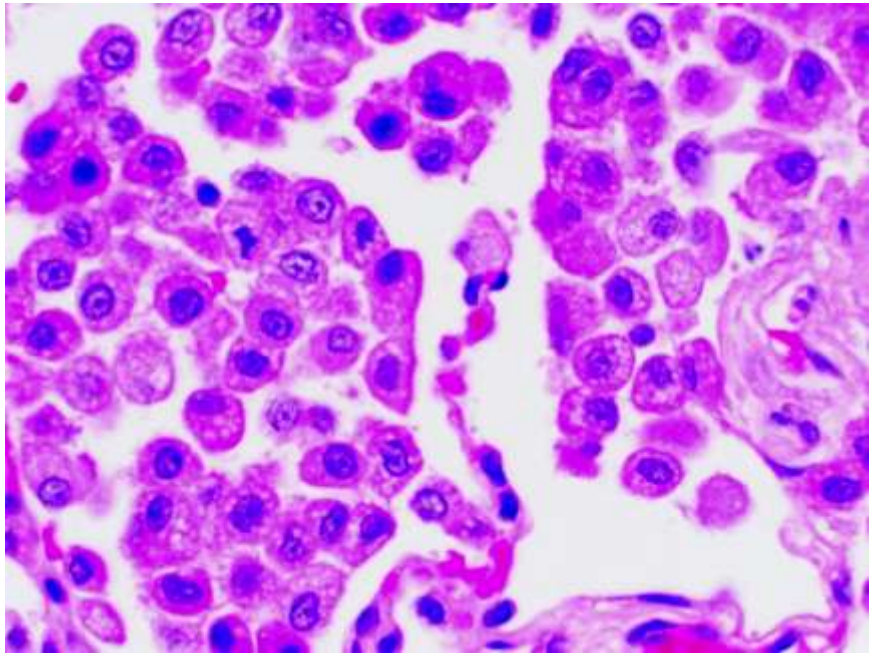


DIP (7 drugs)

- Nitrofurantoin



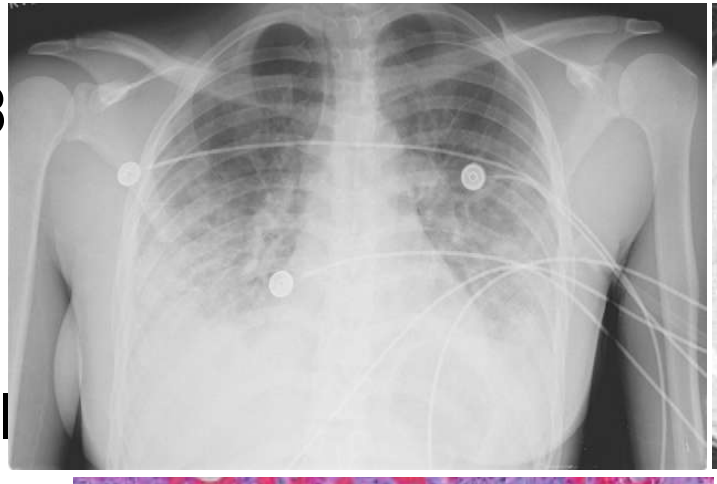


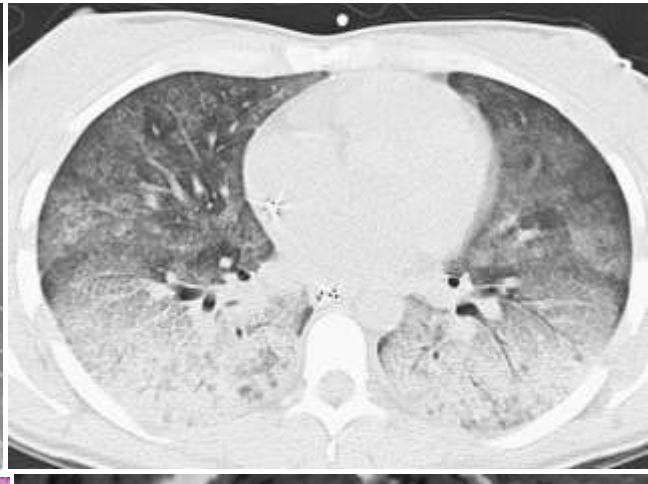


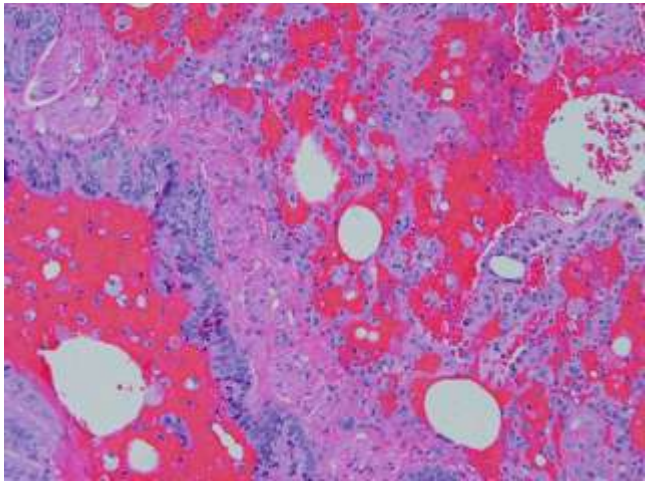
- Amio

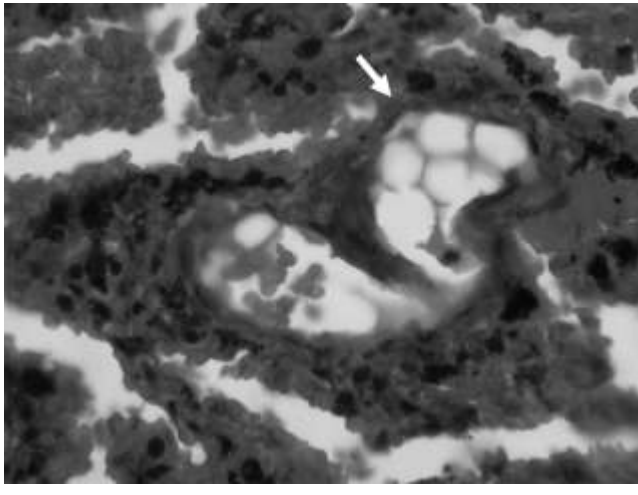
Nonthrombotic pulmonary embolism

- **Fluid slicone (Schmid 2005)**
  - Hypoxemia: 92%
  - DAH: 64%
  - Hemoptysis: 3
  - Fatality rate
    - 8/33
    - 6/6 if neurol symptoms present

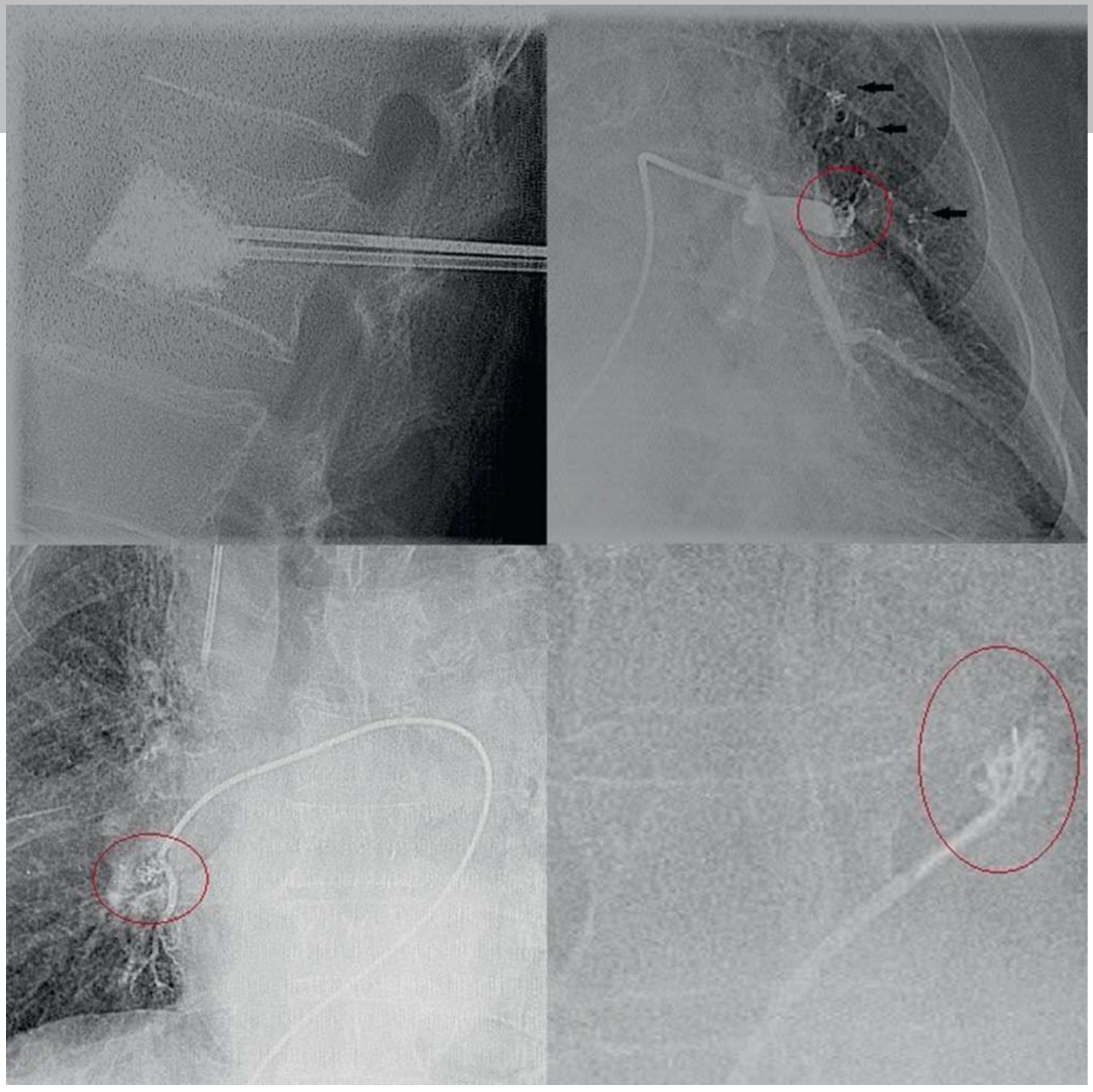








- **Acrylate cement**



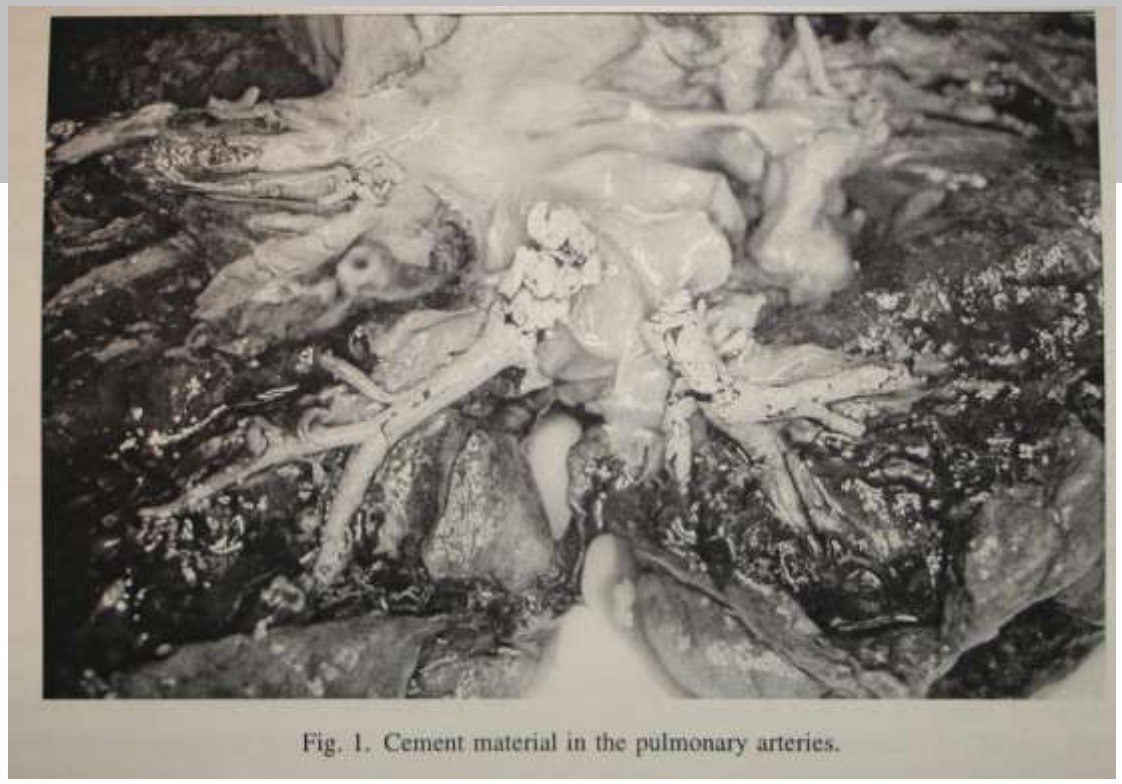
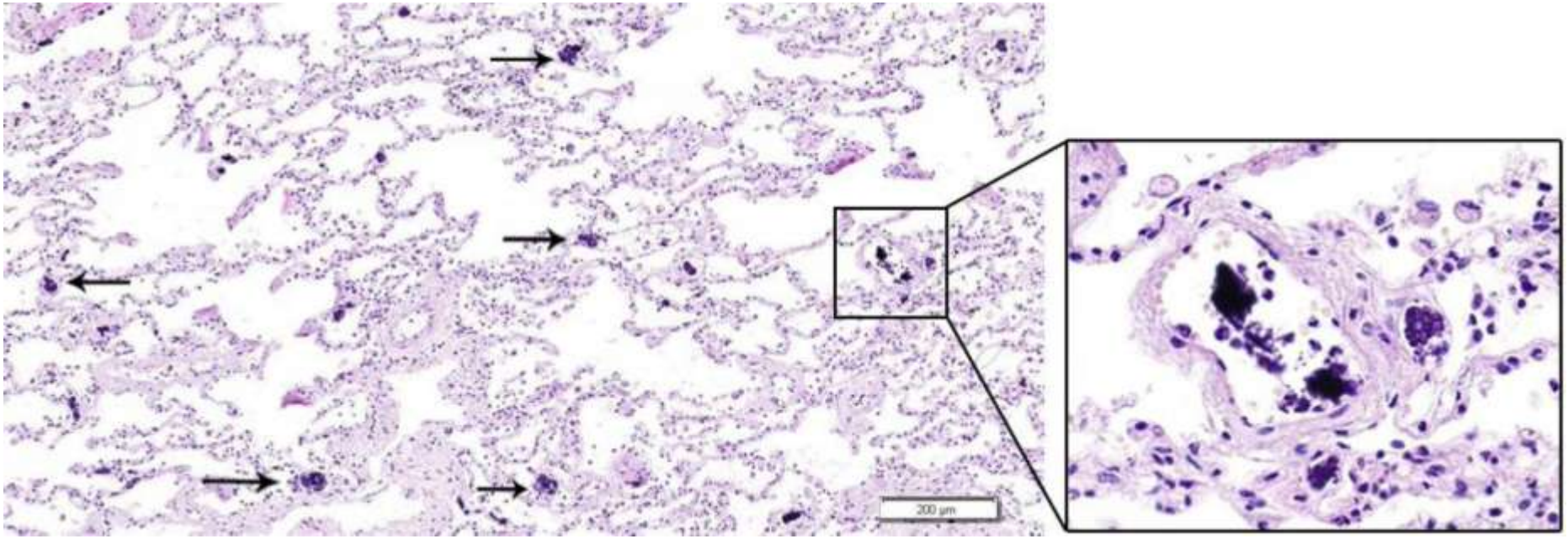
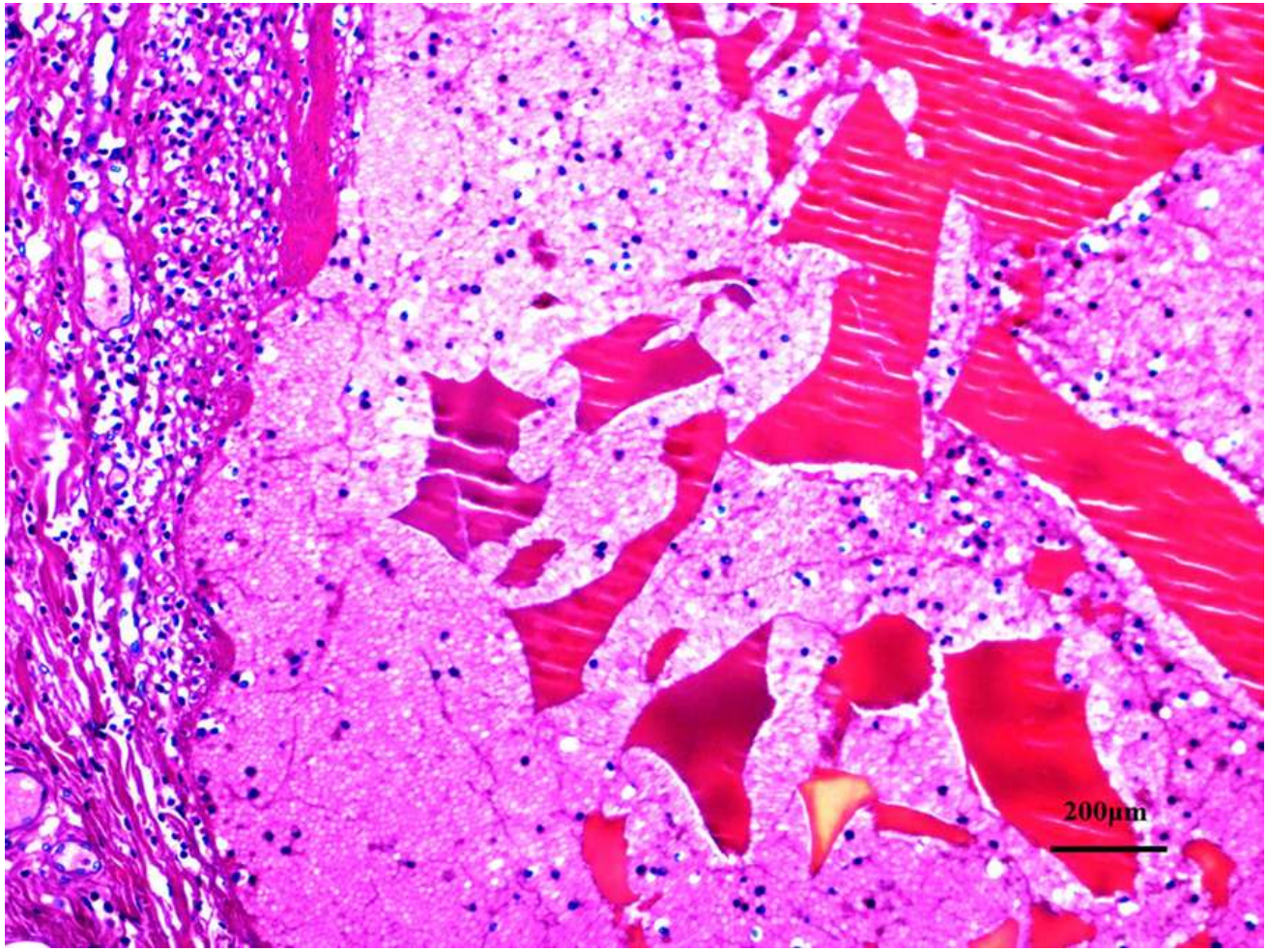


Fig. 1. Cement material in the pulmonary arteries.



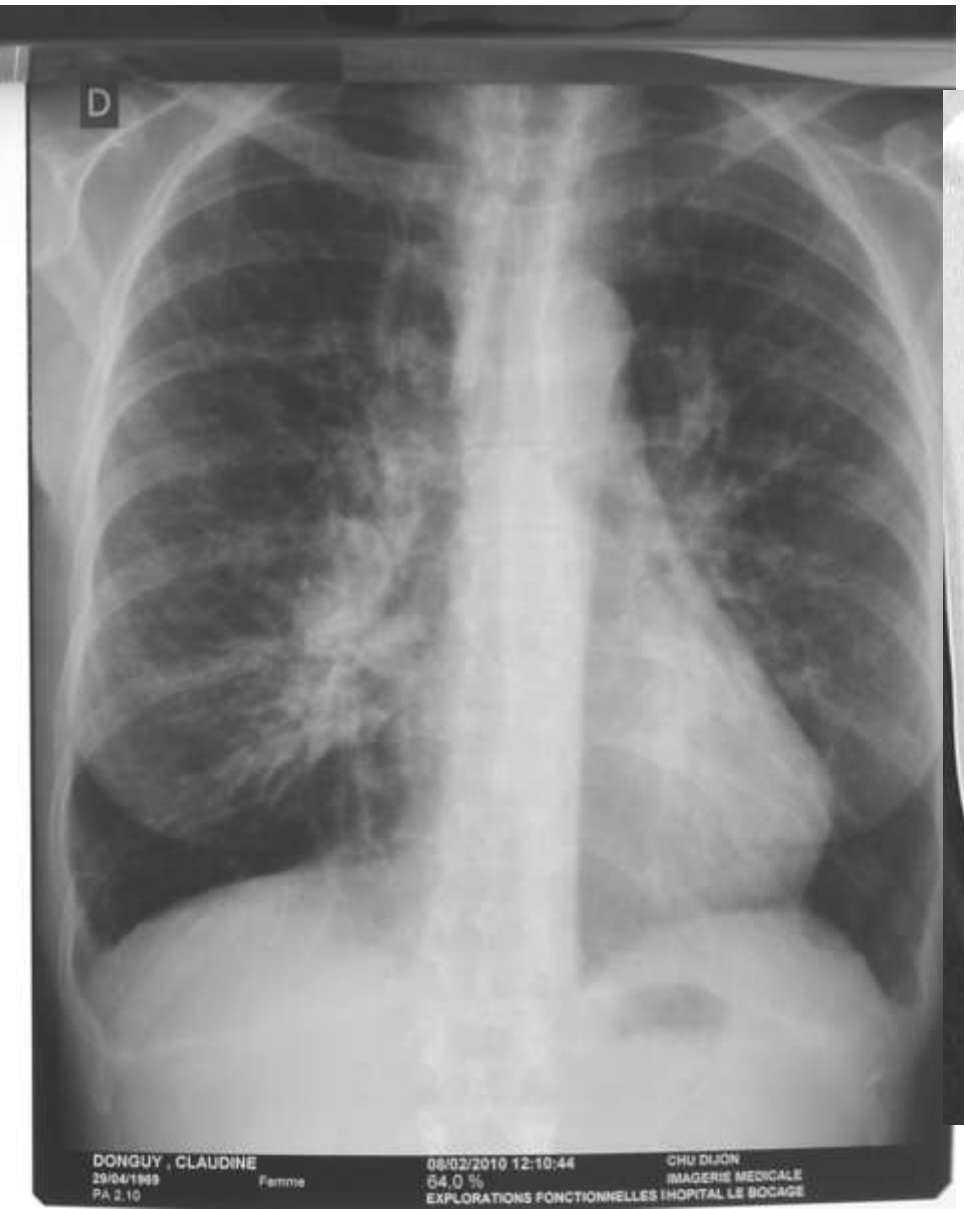
- Hydrogel
- Hyaluronate



DI systemic conditions with possible ILD

- **Goodpasture's**
  - Lazor *et al.*, Medicine 2007: 28 cases
  - Tobacco 89%
    - Cocaine 4
    - Marijuana 3
    - Heroin 1
    - Diesel 1
    - Insecticide 1
    - Tear gas 1

- **Sarcoid-like condition**
  - May mimic sarcoidosis (Chest, deep-seated organs, skin, hypercalcemia)
  - Anti-TNF agents: etanercept
  - Interferon alpha, beta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DONGUY , CLAUDINE
29/04/1969
Femme
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EXPLORATIONS FONCTIONNELLES
CHU DIJON
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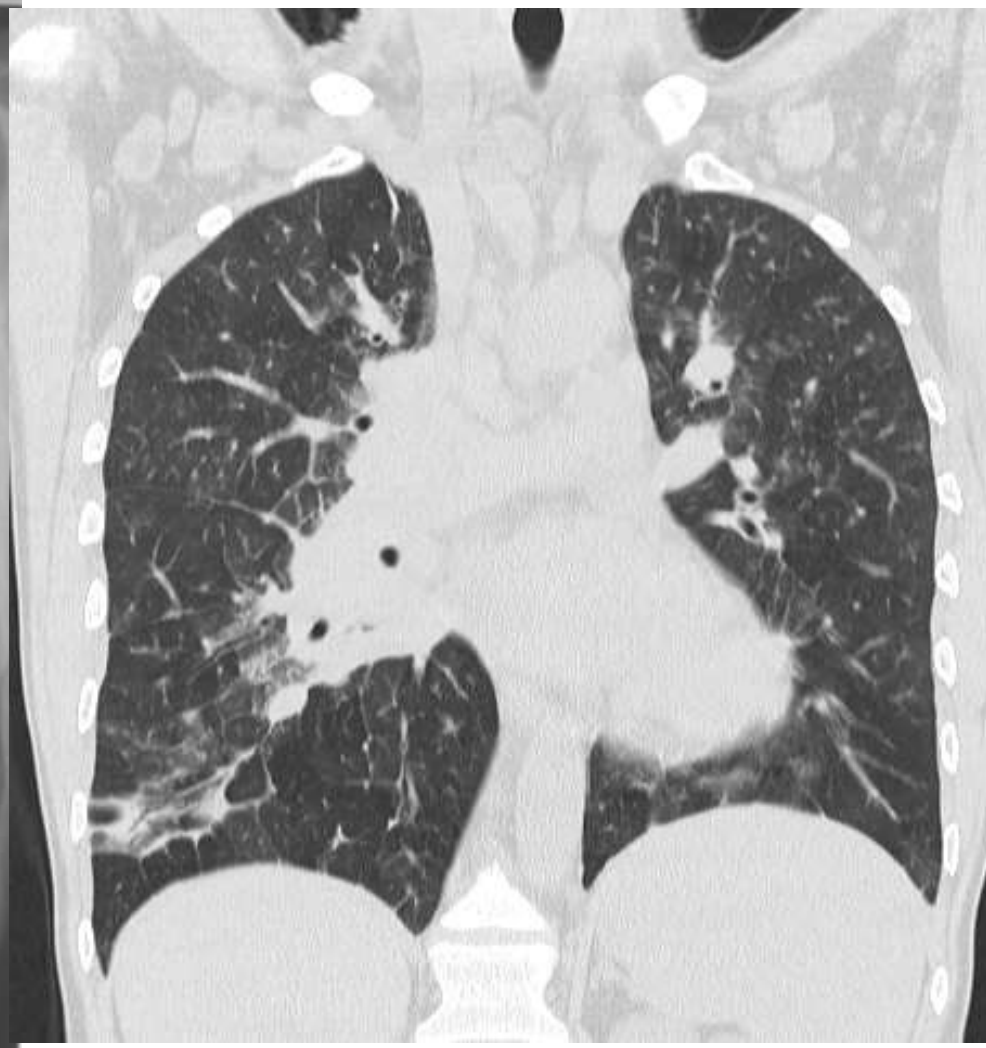
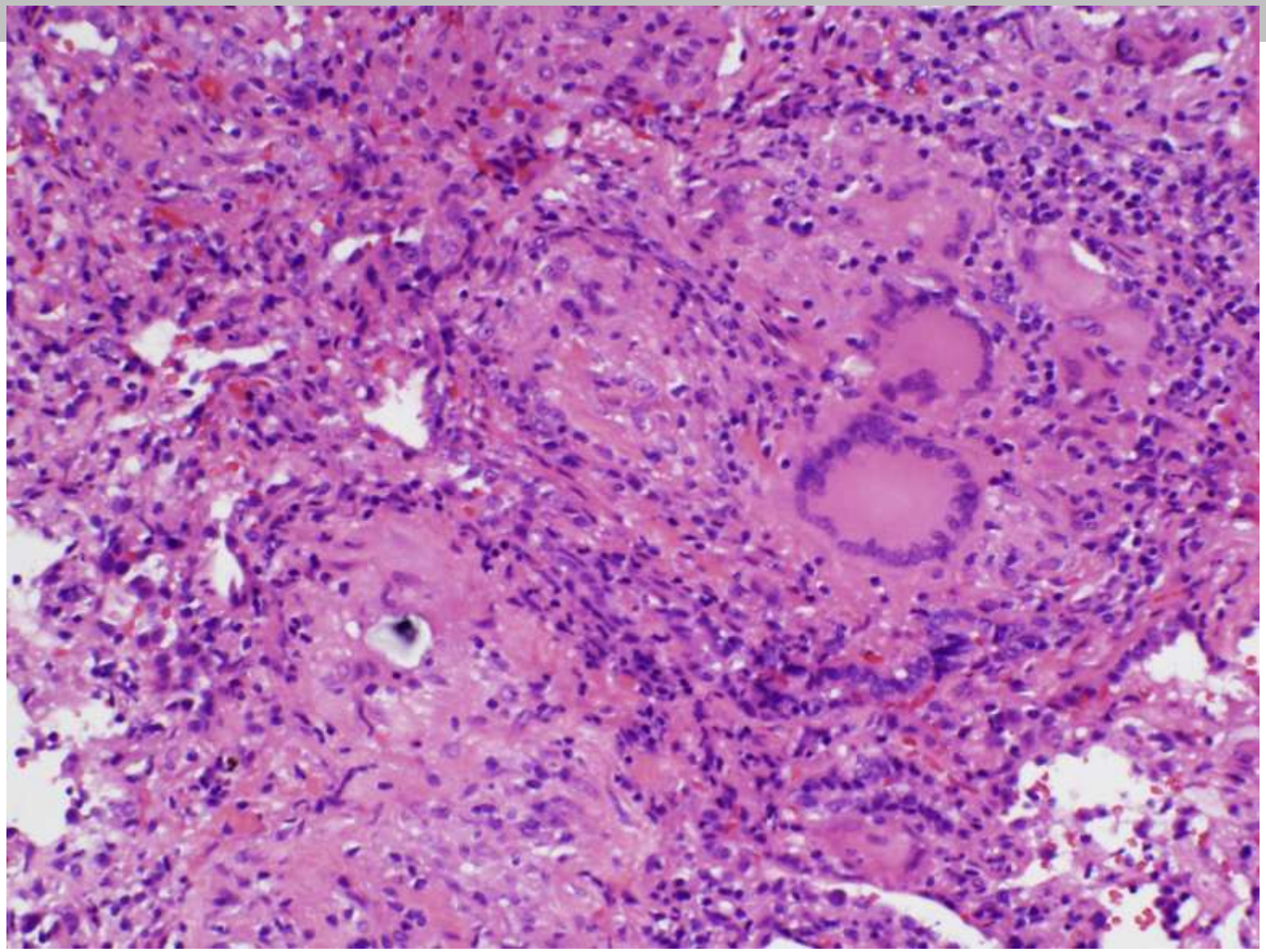
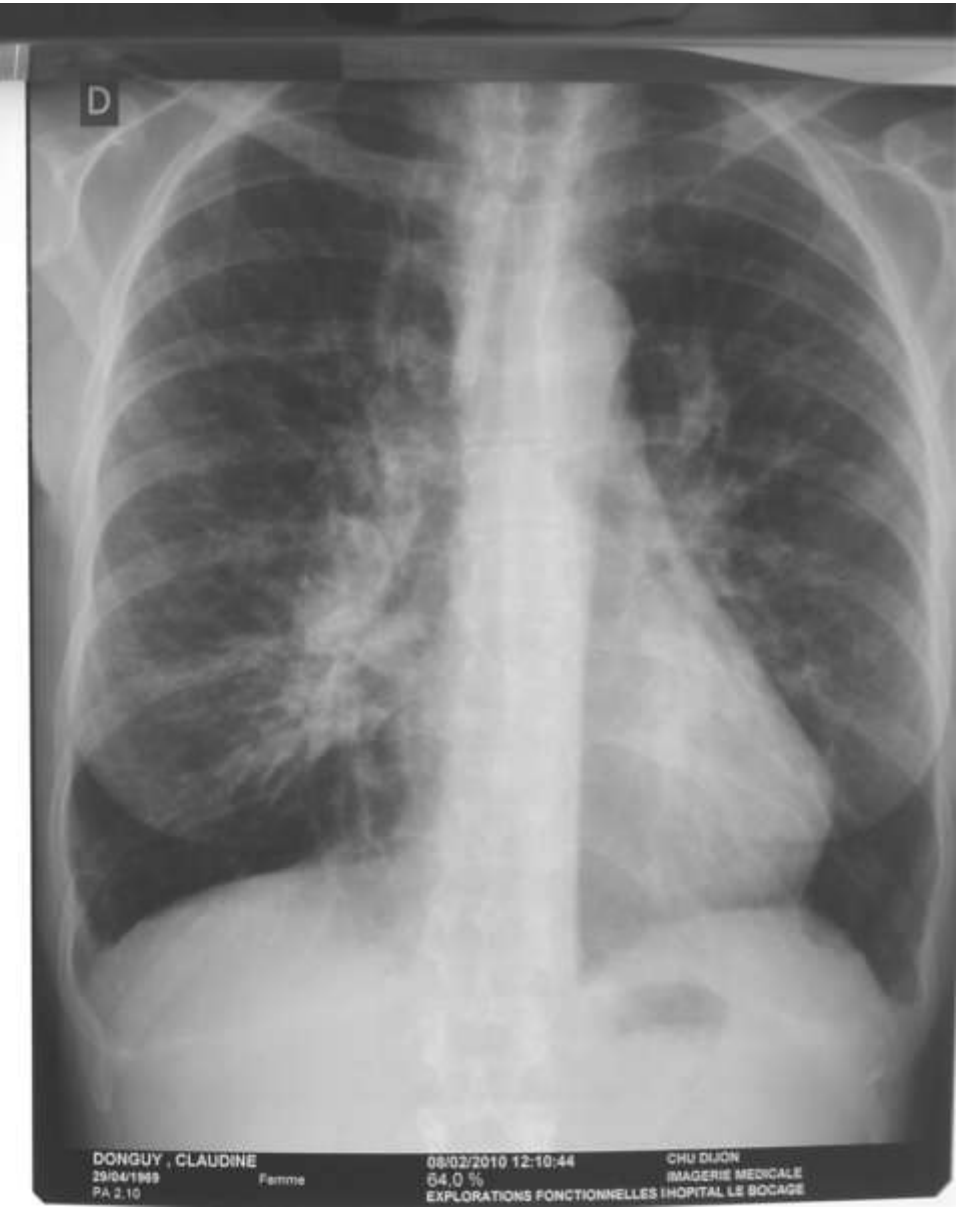
HOPITAL LE BOCAGE





- Courtesy TV Colby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DONGUY , CLAUDINE
29/04/1969
Femme
PA 2.10
08/02/2010 12:10:44
64,0 %
EXPLORATIONS FONCTIONNELLES
CHU DIJON
IMAGERIE MEDICALE
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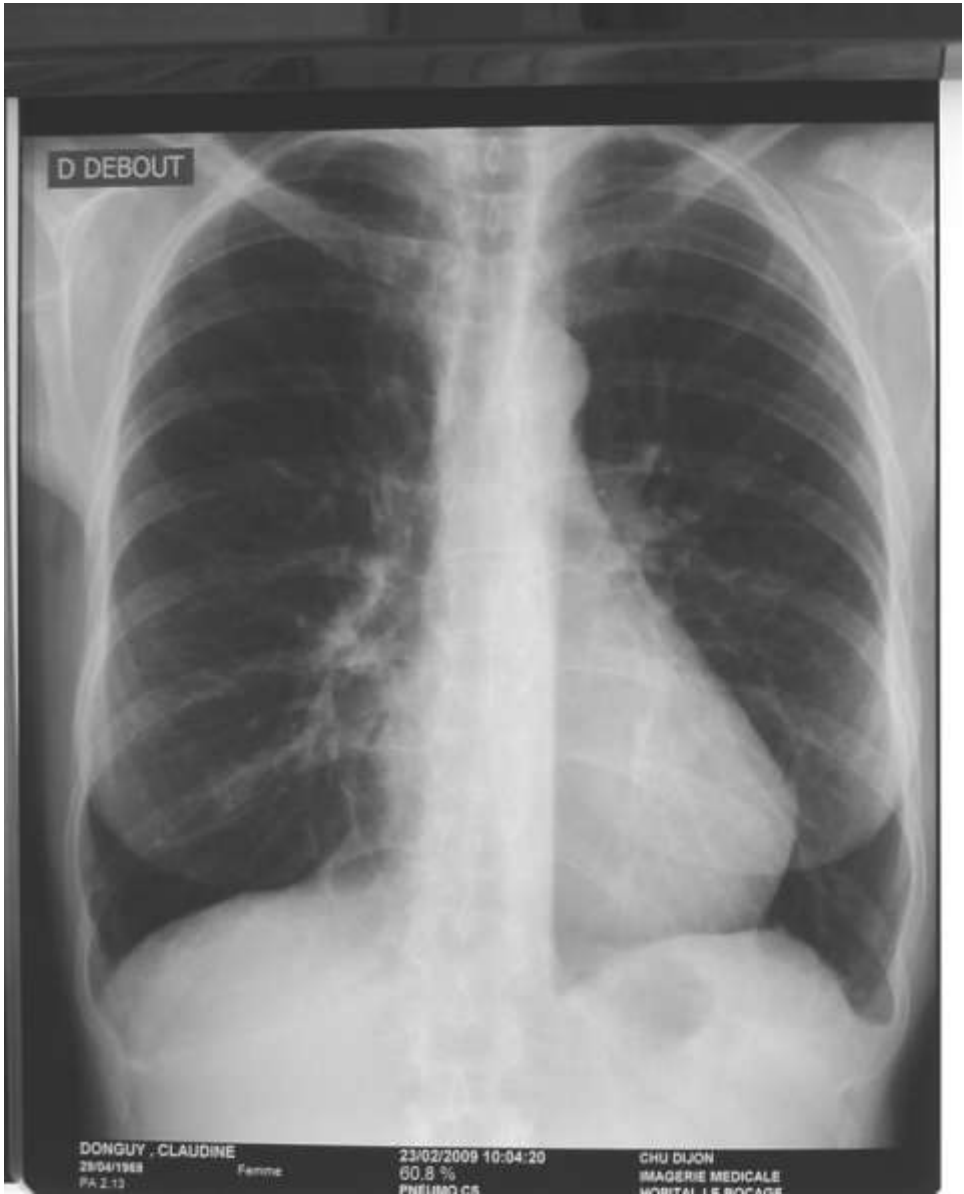
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DONGUY , CLAUDINE
29/04/1969
Femme
PA 2.12
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60.8 %
CHU DIJON
IMAGERIE MEDICALE

DI-ANCA-related systemic conditions

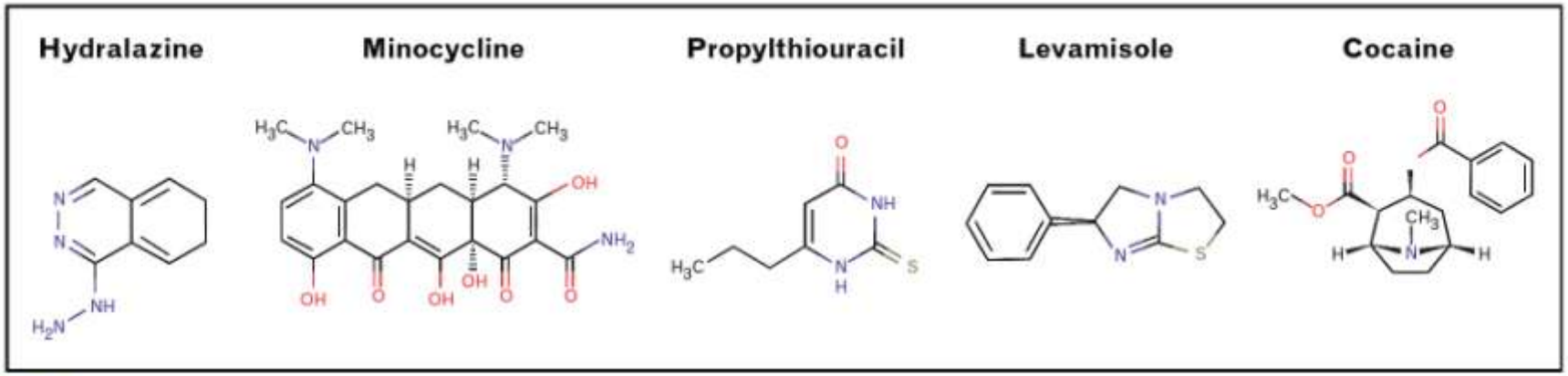


FIGURE 1. Chemical structures of hydralazine, minocycline, propylthiouracil (PTU), levamisole and cocaine. There is a paucity of information regarding structural similarities and differences of these compounds in the literature; therefore, they are represented here for visual review (created using DrugBank).

	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

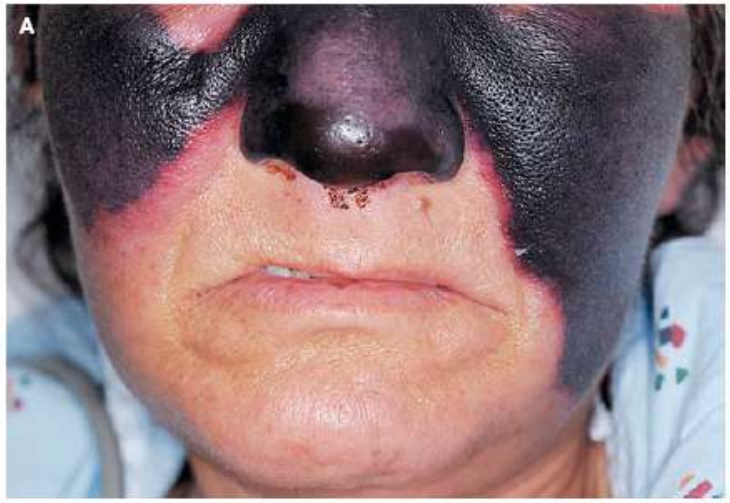
Pendergraft *et al*. 2014

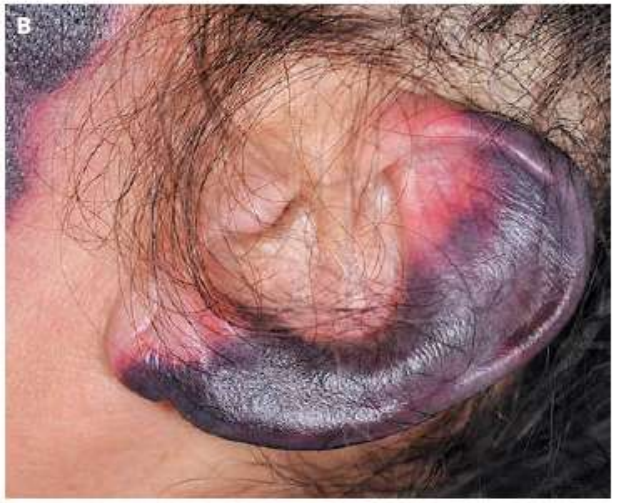
Table 1. Clinical characteristics of ANCA vasculitis associated with hydralazine, minocycline, propylthiouracil (PTU) and levamisole-adulterated cocaine

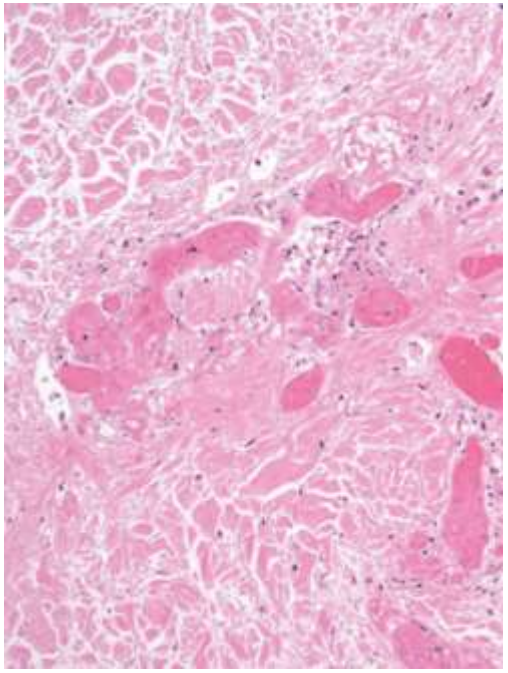
	Hydralazine	Minocycline	PTU	Levamisole-adulterated cocaine
Indication for use	Hypertension	Acne vulgaris	Hyperthyroidism	Illicit euphoric agent
	Heart failure	Tick-borne disease		
Mechanism(s) of action	SM relaxation	Inhibits bacterial protein synthesis	Prevents TG iodination and T4 → T3 conversion	Serotonin-norepinephrine-dopamine reuptake inhibitor[a]
Sex most affected	M ~ F	M ~ F	F > M	M ~ F
Age most affected	Middle-aged to elderly	Adolescents, young adults	Young to middle-aged adults	Middle-aged
Drug duration at time of disease onset	Variable	Variable	Variable	Variable
Signs and symptoms	Arthralgias, rash, dyspnea	PAN	Fever, arthralgias, rash, agranulocytosis[b]	Fever, arthralgias, myalgias, painful and purpuric rash
Organs involved	S, L, K	S, A	S, J, L, K, H^{PMN}	S, J, UA, L, H^{PMN}, K
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
Antinuclear Abs (ANA)	+	+	+	+
Anti-dsDNA Abs	+	–	–	+
Antihistone Abs	+	–	+/–	Unknown
Antiphospholipid Abs	+/–	–	+/–	+
Other ANCA autoantigens	HNE, lactoferrin	HNE, cathepsin G, BPI	HNE. lactoferrin, BPI, azurocidin, cathepsin G	HNE, cathepsin G, lactoferrin
Treatment[c]	Withdrawal	Withdrawal	Withdrawal	Withdrawal
	Extensive	Variable	Variable	Variable
Continue drug?	No	No	No	No
Use drug in future?	No	No	No	No
Alternative agents	Any other class	Doxycycline	Methimazole	Not applicable
Biomarkers	None	None	None	Urine cocaine and levamisole

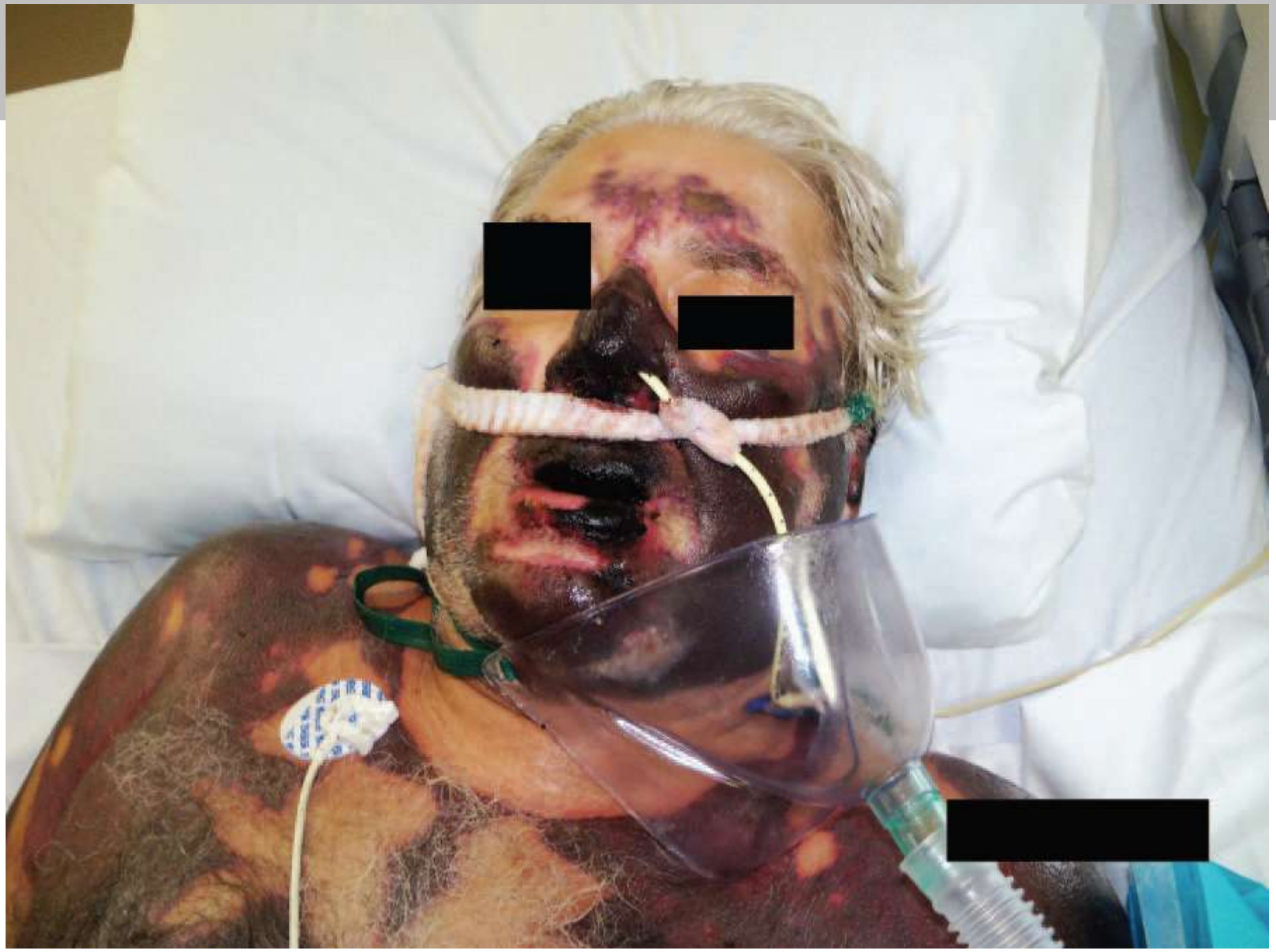
- Levamisole (ANCA-positive cutaneous vasculopathy)

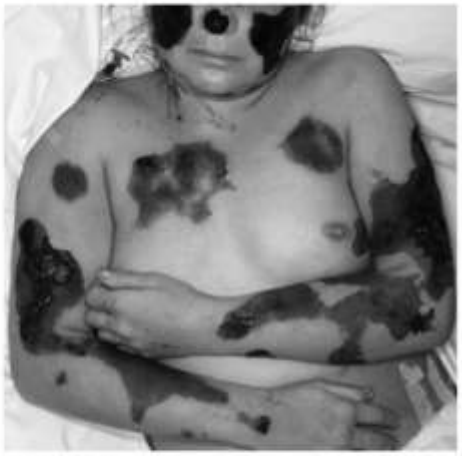
Toxic Effects of Levamisole in a Cocaine User

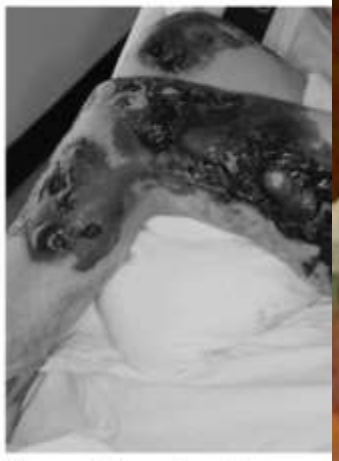












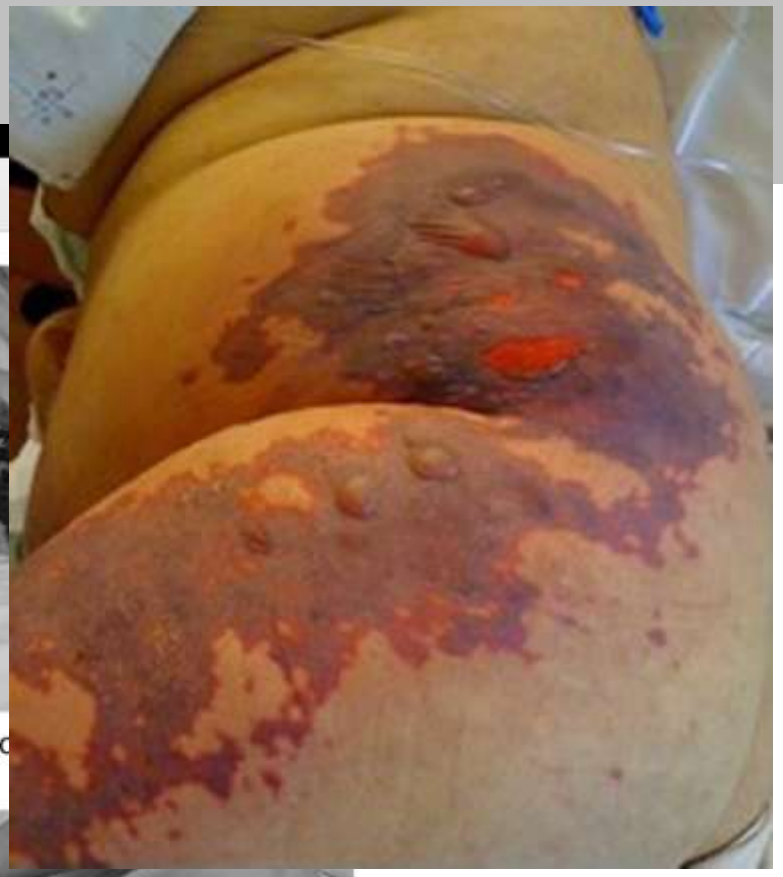
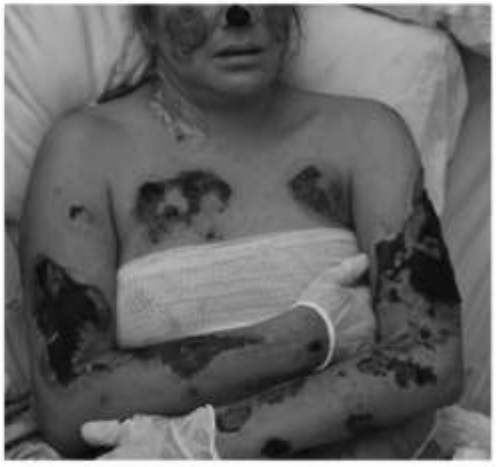


FIGURE 1. Cutaneous defects 4 and 16 days from allegedly smoking free-base co



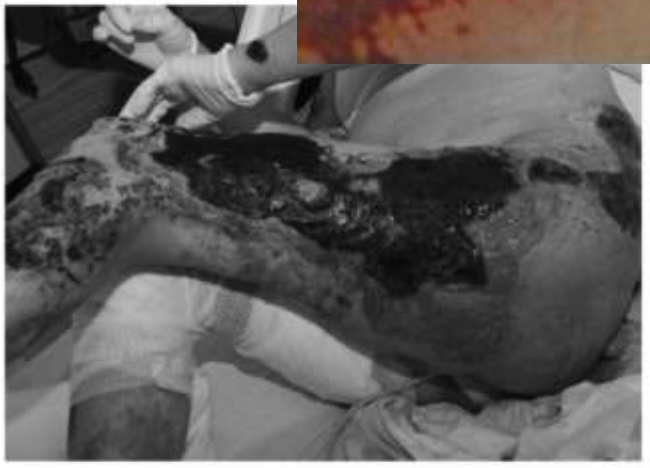


FIGURE 2. Cutaneous defects 16 and 28 days from allegedly smoking free-base cocaine.

Conclusions

- **Drugs are a common consderation in ILD**
  - Extend in bizarre and systemic conditions
- **Diagnosis more often raised than proved**
- **Pathology not necessary in every case**
  - Diagnosctic of: rarely
  - Consistent with: quite often
  - Noncontributory: often
  - May help exclude any incidental condition
- **Careful exclusion of an infection**
- **Prudent drug withdrawal indicated**
- **Watch cryotherapy development**