DIU Paris VII-2017

Pneumopathies interstitielles iatrogènes

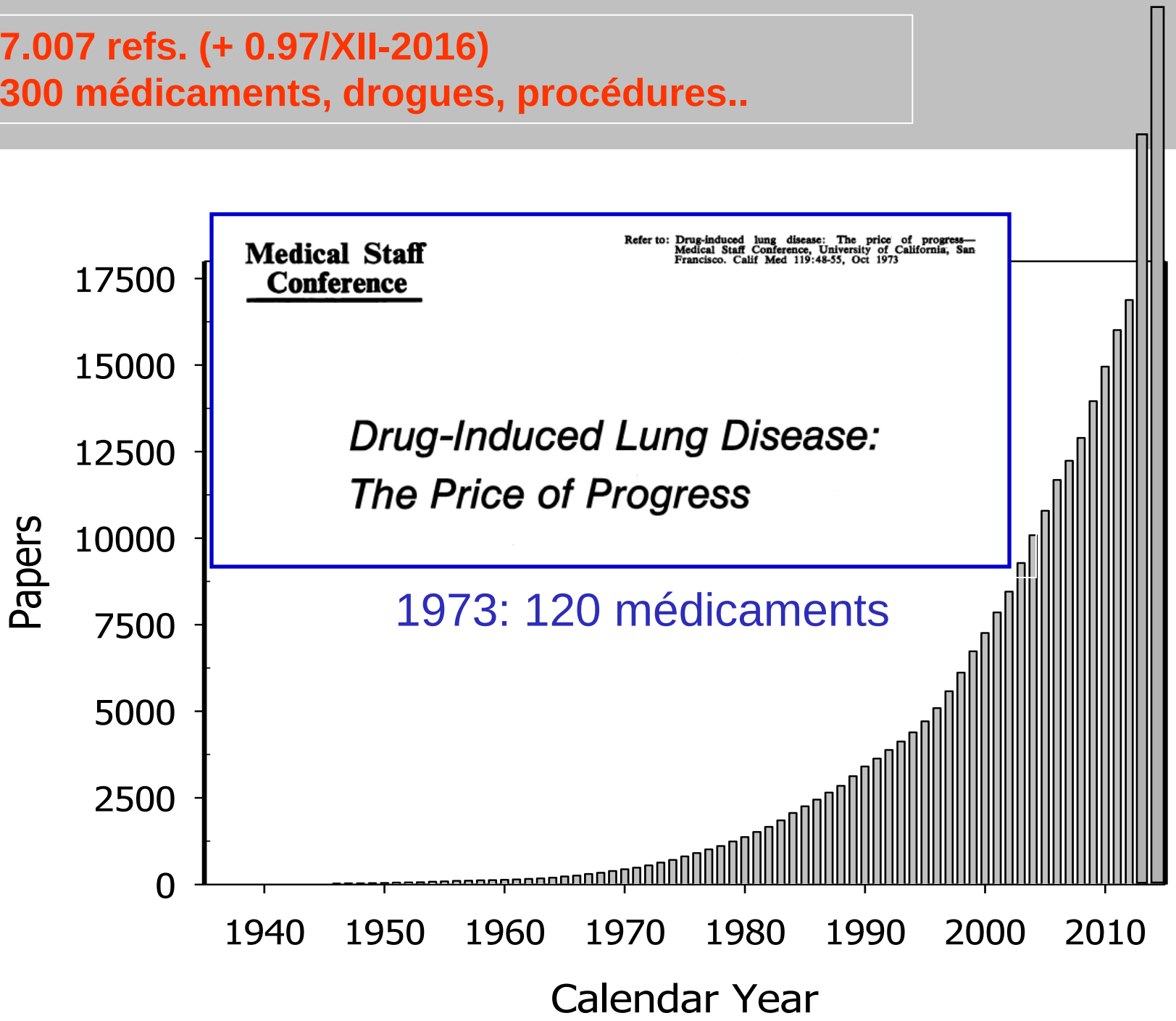
Service de Pneumologie et Réanimation Respiratoire
Hôpital du Bocage - CHU Dijon-Bourgogne
& Université de Bourgogne

www.pneumotox.com

DSMB: Bayer, Onxeo, Roche

- <1980: assez simple (pharmacopée, monothérapies)
  - PnP – fibroses M: bleomycine, alkylants,nitrofurantoïne
  - EoP/PIE: AINS
  - Pleurésies M: ergots (methysergide)
  - PnP huileuse (paraffine)
  - Irradiation
- 1970-1990: methotrexate
- 1980: amiodarone
- 2000 – biothérapies
  - PR
  - Hémato-oncologie - oncologie

27.007 refs. (+ 0.97/XII-2016)
1300 médicaments, drogues, procédures..

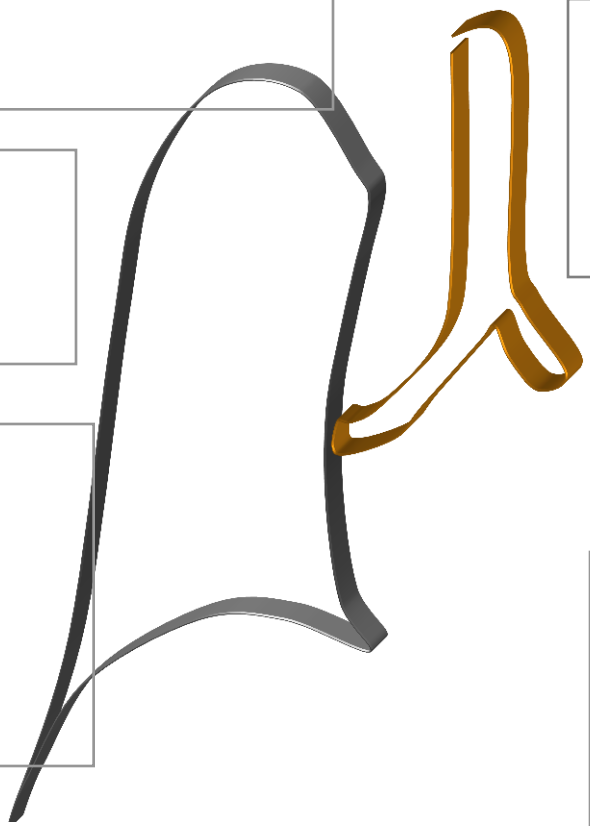


Lung parenchyma ~75%
NSIP (cellular/fibrotic)
DAD
Pulmonary edema
DAH
Opportunistic infection

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

PNEUMOTOX ON LINE

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

ACE inhibitors (ACEI) — 5

I.b I.c IV.a IV.d V.a V.b V.d VIII.a VIII.q IX.e X.d XVIII.k

ATRA — 4

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

Abacavir — 2

I.a I.f II.a II.b IV.d X.a XV.d

Abciximab — 3

III.a X.f

Acebutolol — 2

I.b I.d V.a V.d

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

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

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

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

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

Abciximab — 3
III.a X.f

Acebutolol — 2
I.b I.d V.a V.d

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

J Hematol Oncol. 2009 Nov 12;2:46. doi: 10.1186/1756-8722-2-46.

The occurrence and management of fluid retention associated with TKI therapy in CML, with a focus on dasatinib.

Masiello D, Gorospe G 3rd, Yang AS.

Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases, University of Southern California Medical Center, 1441 Eastlake Ave Suite 7317, Los Angeles, CA 90033, USA. masiello@usc.edu

Abstract

Tyrosine kinase inhibitors (TKIs) like dasatinib and nilotinib are indicated as second-line treatment for chronic myeloid leukemia resistant or intolerant to the current first-line TKI imatinib. These are agents are well tolerated, but potent and as such should be monitored for potentially serious side-effects like fluid retention and pleural effusions. Here we present key clinical trial data and safety considerations for all FDA approved TKIs in context for effective management of fluid retention and pleural effusions. Altering the dasatinib regimen from 70 mg twice daily to 100 mg daily reduces the risk of pleural effusion for patients taking dasatinib. Should pleural effusion develop, dasatinib should be interrupted until the condition resolves. Patients with a history of pleural effusion risk factors should be monitored closely while taking dasatinib. Patients receiving imatinib and nilotinib are not without risk of fluid retention. All patients should also be educated to recognize and report key symptoms of fluid retention or pleural effusion. Pleural effusions are generally managed by dose interruption/reduction and other supportive measures in patients with chronic myeloid leukemia receiving dasatinib therapy.

PMID: 19909541 [PubMed - indexed for MEDLINE] PMCID: PMC2785832 Free PMC Article

Journal of Hematology & Oncology

BioMed Central

Review

Open Access

The occurrence and management of fluid retention associated with TKI therapy in CML, with a focus on dasatinib

David Masiello, Gerry Gorospe III and Allen S Yang*

Address: Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases, University of Southern California Medical Center, 1441 Eastlake Ave Suite 7317, Los Angeles, CA 90033, USA

Email: David Masiello - masiello@usc.edu; Gerry Gorospe - gorospe@usc.edu; Allen S Yang* - allenyan@usc.edu

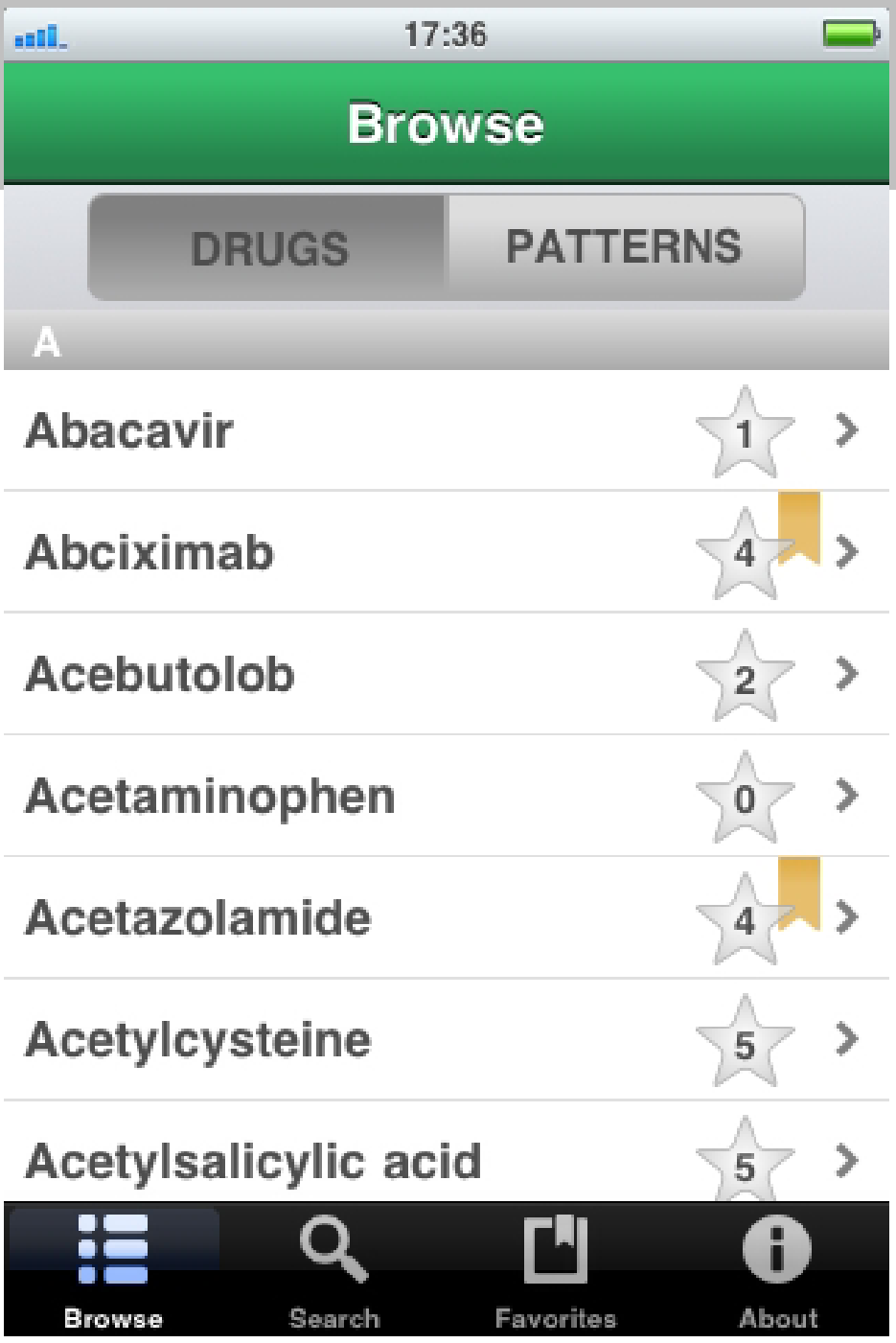
* Corresponding author

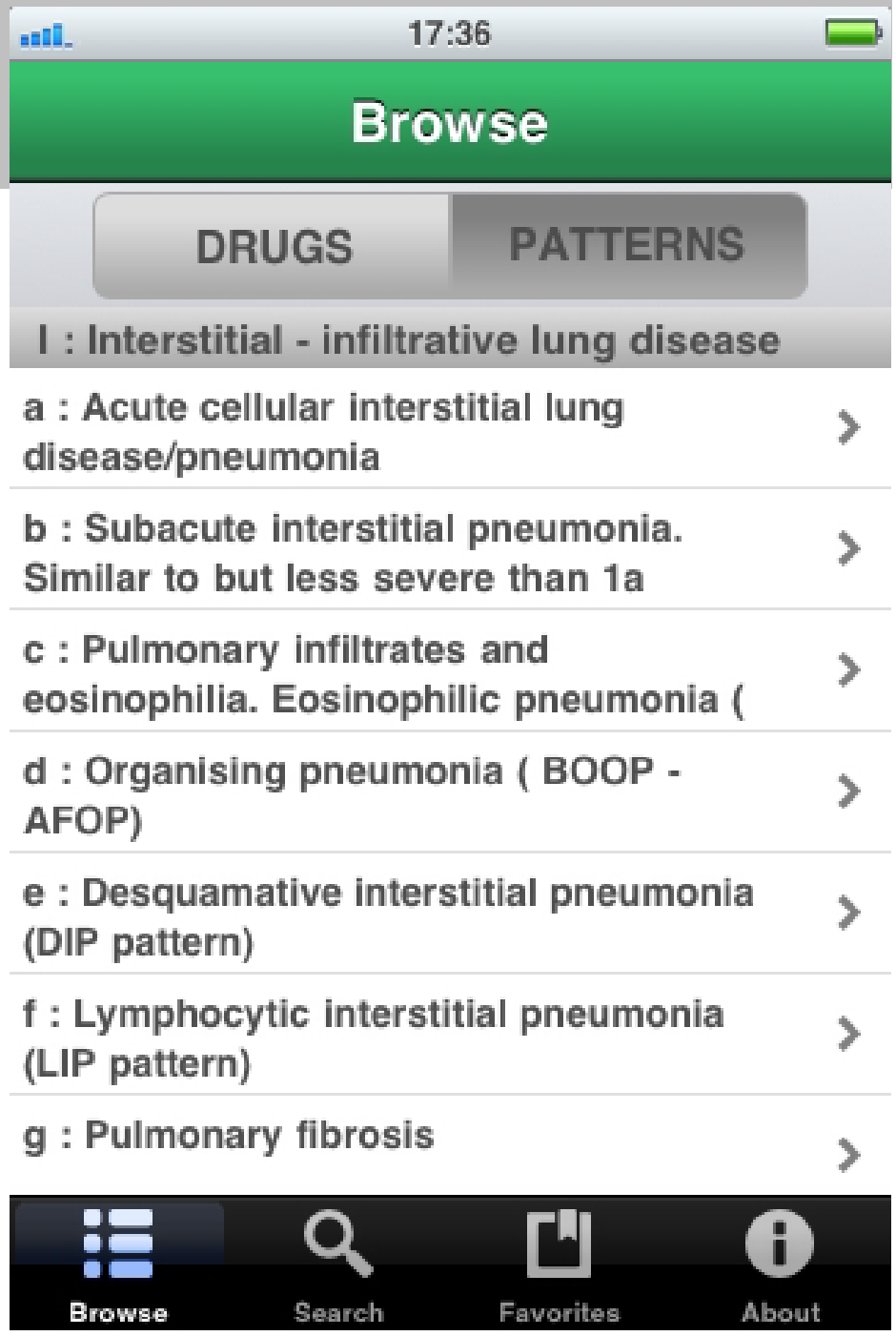
Published: 12 November 2009

Journal of Hematology & Oncology 2009, **2**:46 doi:10.1186/1756-8722-2-46

Received: 28 August 2009
Accepted: 12 November 2009

This article is available from: http://www.jhoonline.org/content/2/1/46


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

Disciplines Impliquées

- ‘Patterns’
  - X-Médecine interne
  - XII-Cardiovasculaire
  - XVII-Infections
  - XVI-Imagerie
  - XV-Anatomie pathologique
  - XIX-LBA
- Oncologie ICPI (mélanome, RCC, poumon)
- Onco-hématologie (rituximab)
- Rhumatologie (TNF-*i*)
- Dermatologie (ICPI)

- XII (a) - Left ventricular dysfunction/failure
- XII (b) - Valvular heart disease
- XII (c) - Pericardial effusion - Pericarditis
- XII (d) - Myocarditis
- XII (e) - Takotsubo cardiomyopathy
- XII (f) - Cardiomyopathy
- XII (g) - Acute coronary event - Myocardial infarction
- XII (h) - Eosinophilic myocarditis
- XII (i) - Infective endocarditis
- XII (j) - Myocardial stunning
- XII (k) - Pericardial thickening/constriction
- XII (l) - Arrhythmia, dysrhythmia incl. fibrillation
- XII (m) - Cardiac-cardiopulmonary arrest
- XII (n) - Shock, cardiovascular collapse, hypotension
- XII (o) - Coronary artery disease
- XII (p) - Long QT syndrome
- XII (q) - Coarctation of the aorta (acquired)
- XII (r) - Congestive heart failure
- XII (s) - Heart block (bundle or AV)
- XII (t) - 'Torsades de pointe'
- XII (u) - Left-sided intracavitary thrombosis
- XII (v) - Hypertrophic cardiomyopathy
- XII (w) - Asystole
- XII (x) - Sinus arrest
- XII (y) - Pneumopericardium
- XII (z) - Heart valve thrombosis
- XII (aa) - Acute aortic vasoconstriction
- XII (ab) - Pericardial fat necrosis
- XII (ac) - Right atrial thrombosis
- XII (ad) - Effusive-constrictive pericarditis
- XII (ae) - Aortic dissection
- XII (af) - Coronary arterial spasm
- XII (ag) - Bradycardia
- XII (ah) - Endocardial fibroelastosis

Difficultés actuelles

- Nombre de publications
- Fake papers
  - IF divers
  - ‘Open access’ Articles payants pour les auteurs
  - Reviewing quasi-inexistant
  - ‘Big data’ : fiabilité incertaine
  - Critères diagnostiques divers
  - Diagnostic différentiel rudimentaire
    - Médicaments, maladie sous-jacente, infection
  - ILD: fourre-tout
  - BOOP, NSIP, HSP, DAD sur imagerie
  - Modes
  - Crainte: diagnostic en excès et arrêts de ttt intempestifs (MTX+++)

Tomari *et al*. 2016 J Stroke Cerebrovasc Dis (IF: 1.669)

- Patients who developed acute respiratory failure while taking apixaban
- And were subsequently diagnosed as having ILD
- Feb 2013 (release of apixaban in Japan) - May 2015
- Chest computed tomography results were mandatory to make a positive diagnosis.

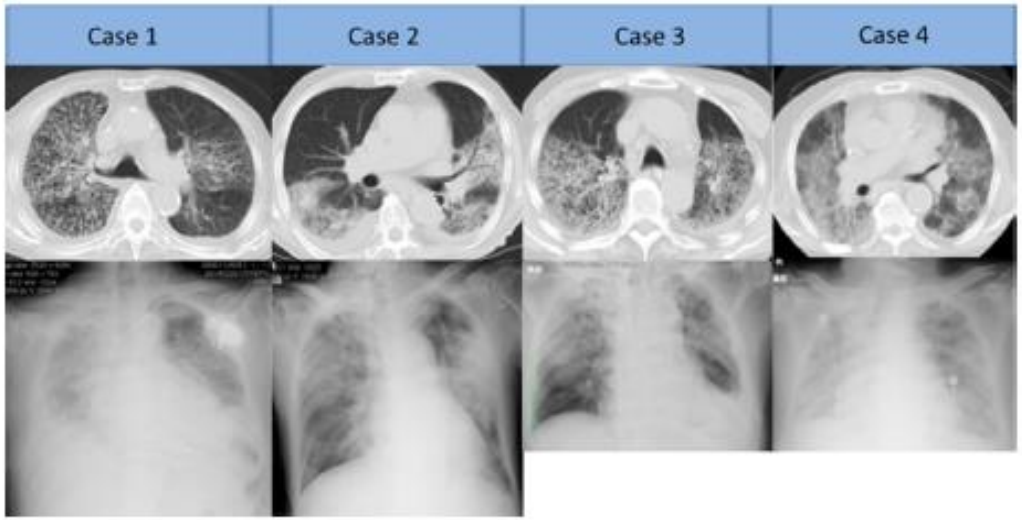


Figure 1. *Chest computed tomography and routine radiography early after symptom onset.*

- Postmarketing surveys conducted up to Feb 2016 in Japan (information from each pharmaceutical company) have recorded ILD in
  - 49 apixaban users
  - 100 rivaroxaban users
  - 68 dabigatran users

Successful Crizotinib Rechallenge After Crizotinib-Induced Interstitial Lung Disease in Patients With Advanced Non–Small-Cell Lung Cancer

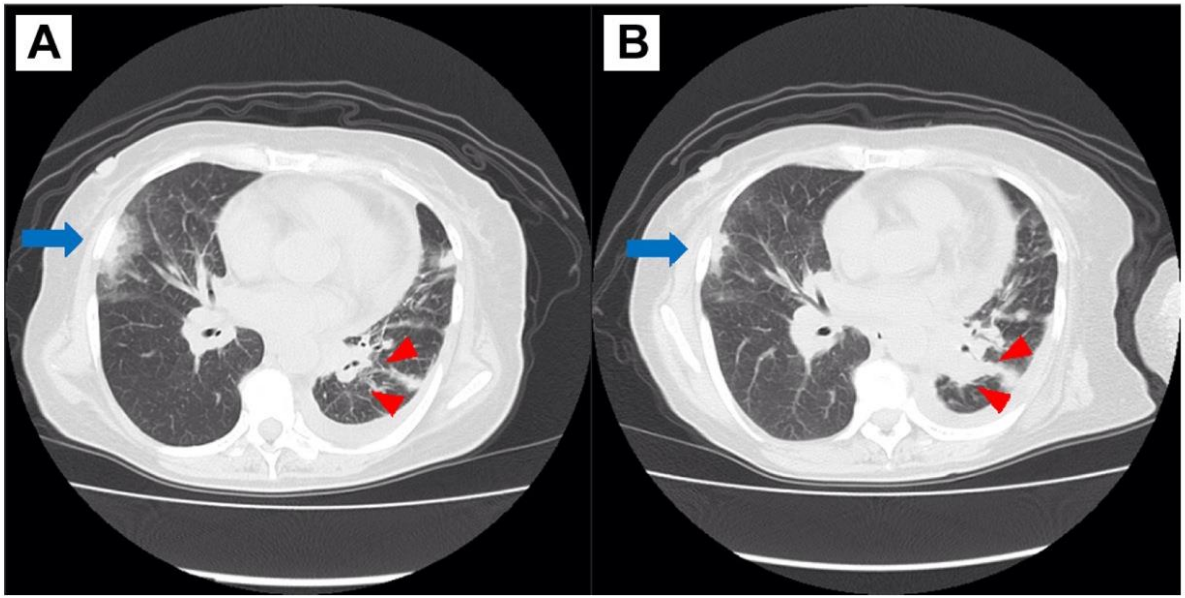
Nobuhiro Asai, Etsuro Yamaguchi, Akihito Kubo

Clinical Practice Points

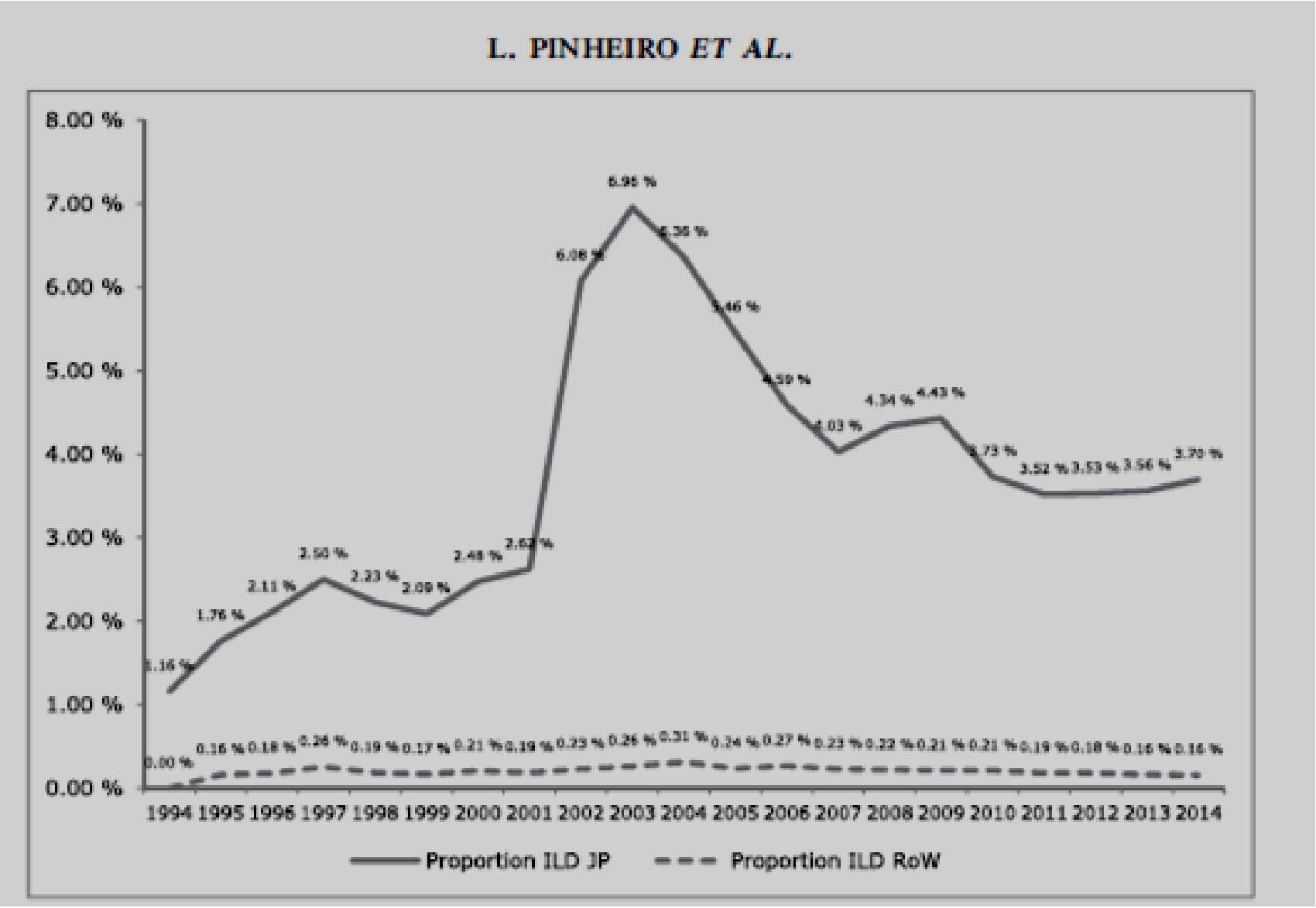
- Although the development of the anaplastic lymphoma kinase tyrosine kinase inhibitor (ALK TKI), as well as epidermal growth factor receptor (EGFR) TKIs, has a great impact and has led to a paradigm shift in the treatment of advanced non–small-cell lung cancer (NSCLC), the occurrence of drug-induced interstitial lung disease (ILD) remains problematic.
- We report a successful rechallenge of crizotinib after crizotinib-induced ILD in a patient with ALK-rearranged NSCLC. To our knowledge, this is the second case successfully treated and the first short review of crizotinib-induced ILD.
- Comparing the 2 successfully treated cases, including ours, with the fatal case previously reported, we found some common characteristics in the successful case and our case, among which was the fact that our patient had no risk of EGFR TKI–induced ILD. The risk factors for EGFR TKI–induced ILD may be related to crizotinib-induced ILD.
- Although crizotinib-induced ILD may be fatal, some patients might benefit from rechallenge of the drug. It is important to elucidate the clinicopathologic characteristics of ALK TKI–induced ILD and to determine its risk factors.

Successful Crizotinib Rechallenge After ILD

Figure 1 (A) Chest Computed Tomography (CT) Showed Crizotinib-Induced Interstitial Lung Disease (ILD) in the Right Upper Lobe of the Lung (Blue Arrow). (B) Two Weeks After Crizotinib was Discontinued, Chest CT Showed That ILD had Improved (Blue Arrow) and That the Tumor Regrew (Red Arrowhead)



Pinheiro *et al*. 2016



BOOP-NSIP-DAD-PHS-Fibrose *sine* pathology

Mesalazine-induced lung fibrosis

Ebraheem Alskaf, Amer Aljoudeh, Frank Edenborough

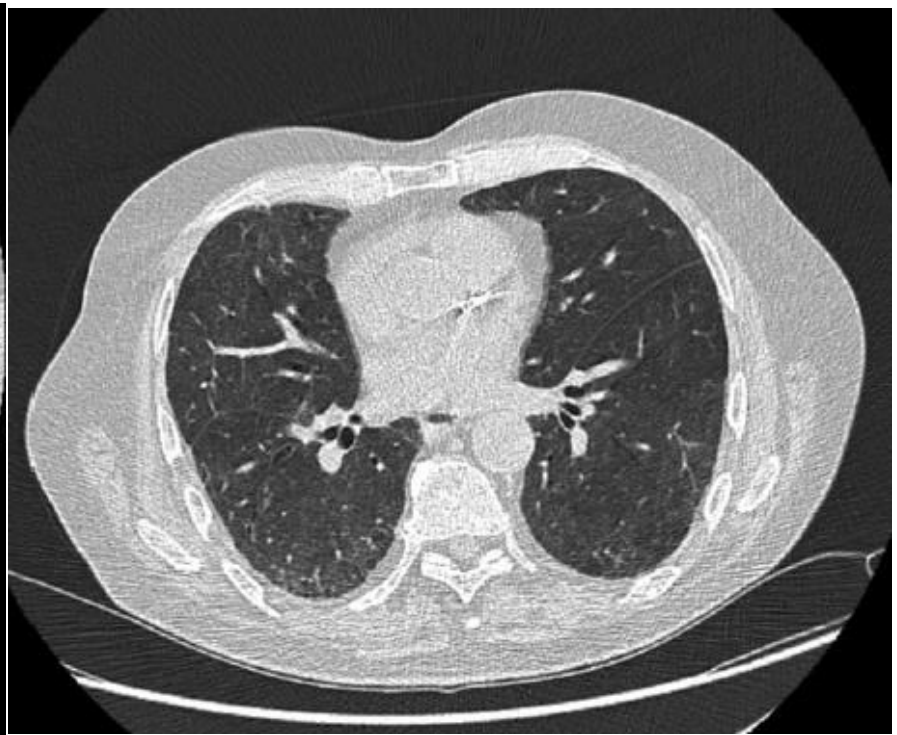


Table 3 – Incidence of DLIs in Japan and abroad.

Drug	Japan	Abroad[a]	
Gefitinib	3.98% ($n=1482$)	0.3% (United States: $n=23,000$)	x13.2
Leflunomide	1.81% ($n=3867$)	0.017% (Abroad: $n=861,860$)	x106
Bleomycin	0.66% ($n=3772$)	0.01% (Abroad: $n=295,800$)	x66
Bortezomib	2.33% ($n=3556$)	0.16% (Abroad: $n=106,832$)	x14.6
Erlotinib	4.52% ($n=3488$)	0.7% (Abroad: $n=4900$)	x6.5

Modified from References [10–12].

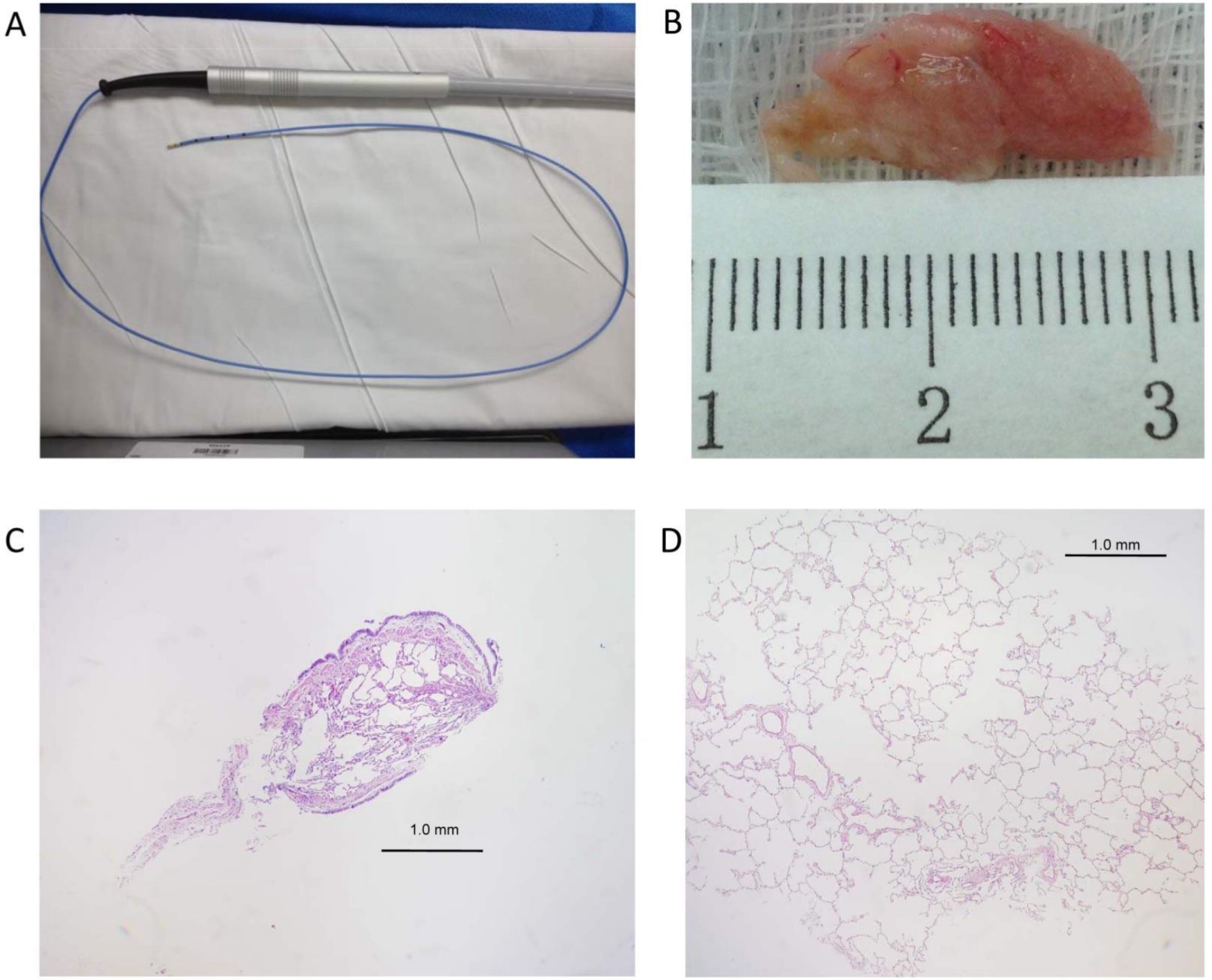
[a] Data for some drugs include data from Japan.

Imagerie – anatomie pathologique

- Cleverley 2002: 20 PnI médicamenteuses
  - Concordance diagnostique: 45%
  - Discordance: 55%
- Blackhall 2013: 103 PnI
  - Concordance diagnostique: 18.4%
  - Discordance: 51.5%
  - Pas de diagnostic: 30.1%
- Kayatta 2013: 194 PnI
  - Concordance diagnostique: 15%
- Donc prudence

Biopsie pulmonaire: risques

- Chirurgicale
  - Patient asymptomatique: 0.6%
  - Patient en IR: 3.5 – 35%
  - Hutchinson et al. 2016
    - Intrahospitalière 1.7%
    - @ 30 j 2.4%
    - @ 90 j 3.9%
- Cryobiopsie
  - 0.1%


A
B
1
2
3
C
1.0 mm
D
1.0 mm

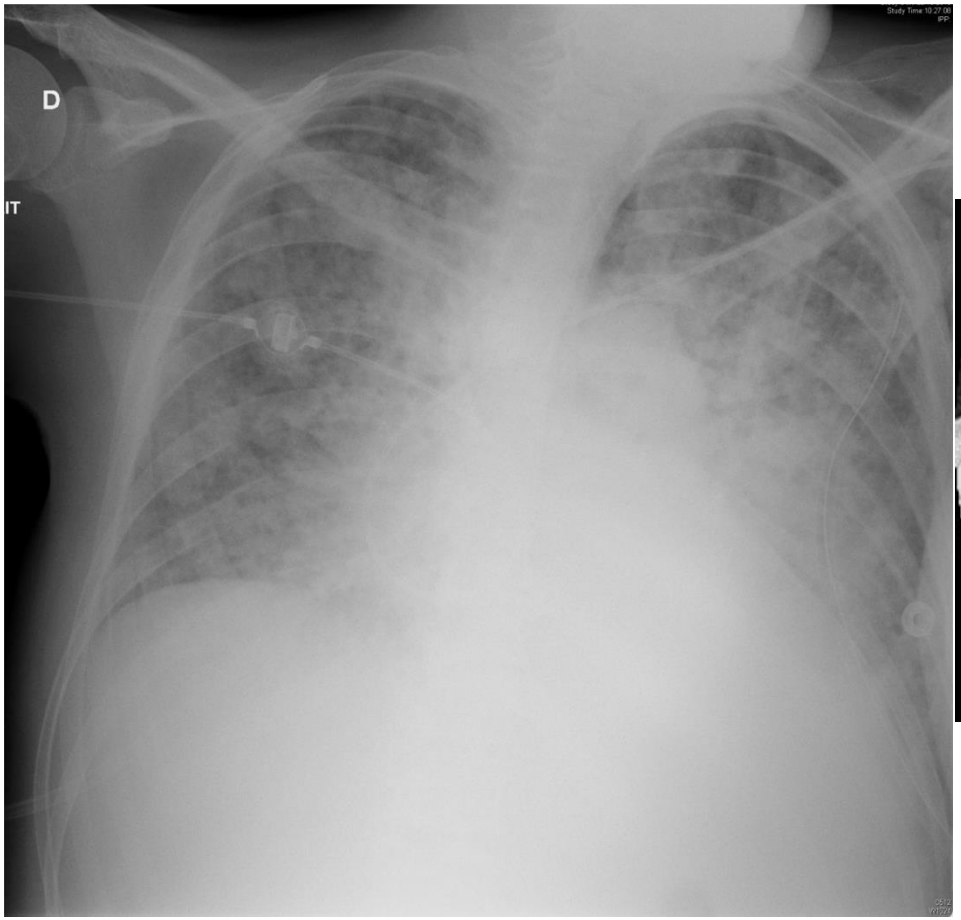
Critères diagnostiques

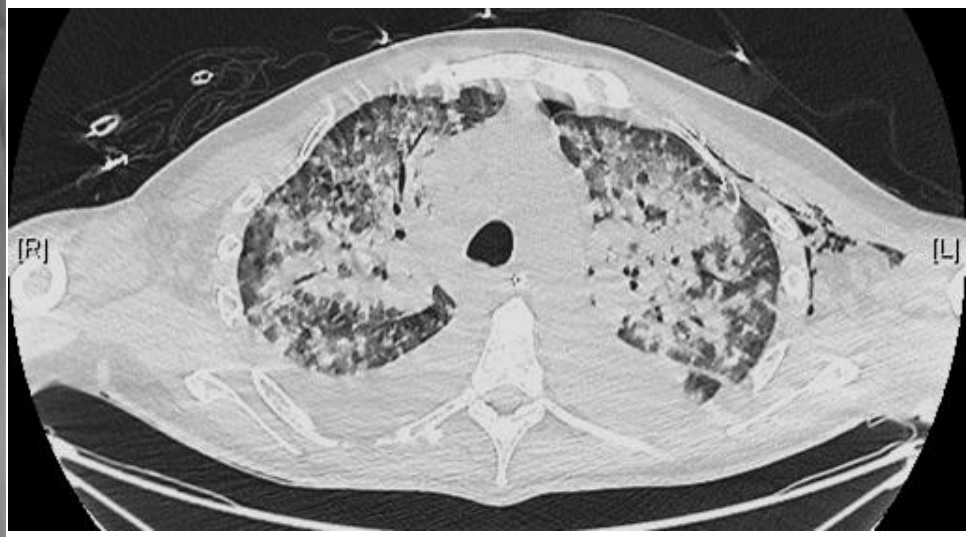
- Exposition
- Chronologie cohérente
- Bilan pulmoniare pré-traitement normal
- Littérature confirmative (nb de cas, niveau de preuve)
- Présentation compatible
- Exclusion de toute autre cause
- Amélioration à l’arrêt du traitement
- Récidive si réexposition…

Checklist ‘aéro’

- Exposition (un ou plusieurs médicaments? Drogues?)
- Exposition précède les symptômes (sec-années)
- Tableau compatible -> Pneumotox
- Qualité du signal dans la littérature: ‘-’ à ‘5’
- Bilan préexistant (normal ?)
- Biomarqeur (BNP, AAN, ANCA)
- Dosage du médicament ?
- Diagnostic différentiel mé-ti-cu-leux
- Discuter éviction
- Discuter reprise du ttt (bénéfice-risque)

- Guinard *et al*. Active tuberculosis in psoriasis patients treated with TNF antagonists: a French nationwide retrospective study. J Eur Acad Dermatol Venereol 2016
  - 8 centres, 2006-2014, 12 cas 9 Ho M=49 ans
  - Infliximab 7, adalimumab 4, certolizumab 1
  - 12/12: Screening TBL effectué
  - Extrapulmonaire : 10/12
  - BK+: 6
  - Délai moyen 23.4 semaines (2-176)
  - Histologie 7 (6 granulomes, 5 nécrose caséeuse)
  - 2 décès: TB disseminée


D
IT


[R]
[L]

-

PnP *Pneumocystis jiroveci* non VIH / VIH

- Prodrômes <7 / 28j
- Début rapide / progressif
- PaO2 50mmHg / 69 mmHg
- CD4+ 100-1000 / très abaissés
- *Pneumocystis* LBA rares / ++/+++
- Mortalité 14-60% / 10%

- Attn! PnP Pj et MTX clinique et imagerie similaires

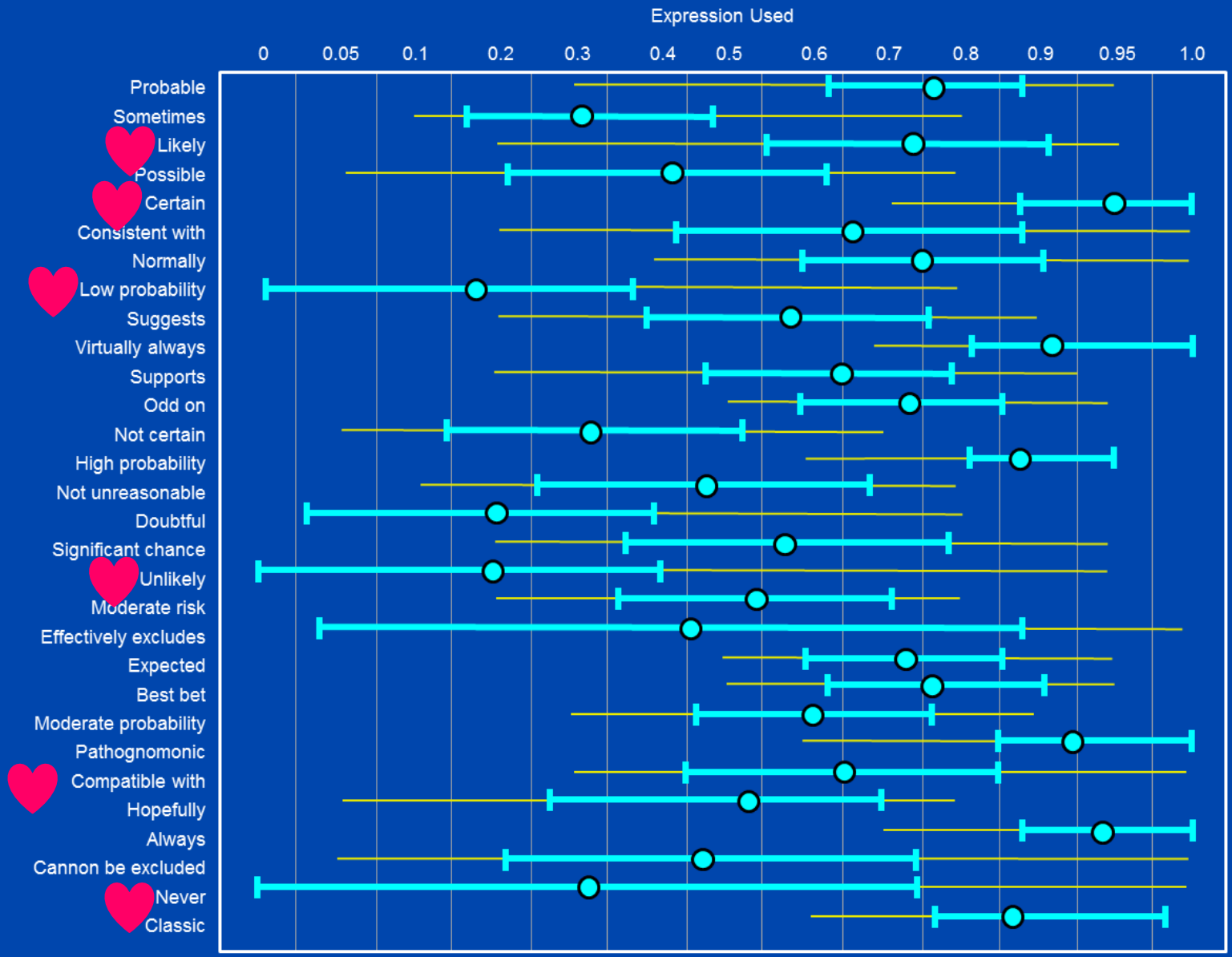
En pratique

- Exclu: 10%
  - On peut continuer le médicament

- *Douteux*
- *Possible*
- *Plausible*
- *Probable*

- Certain: <5%
  - On doit généralement arrêter le médicament
  - Si réintroduction: encadrée et stricte

Subjective Probability Estimates Assigned to Each Expression by 16 Physicians



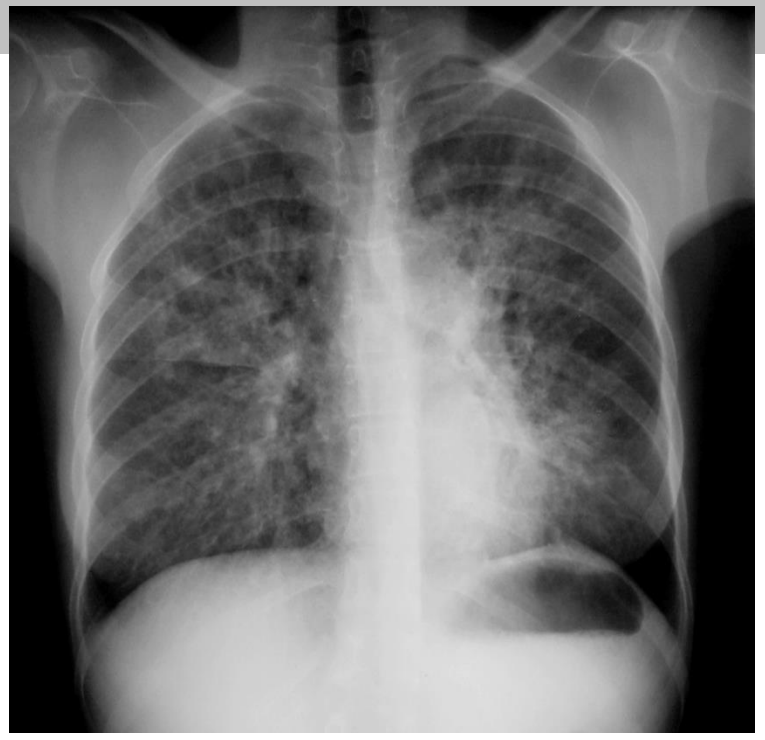
MAYO CLINIC

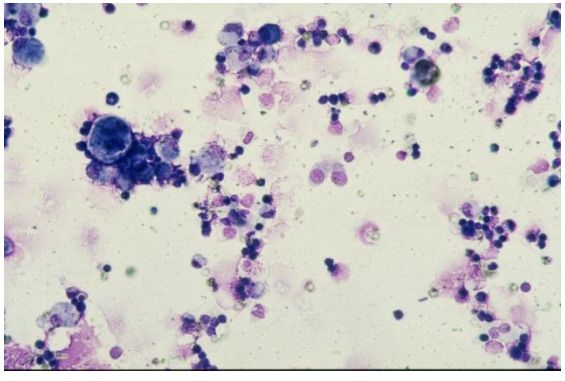
Actualité

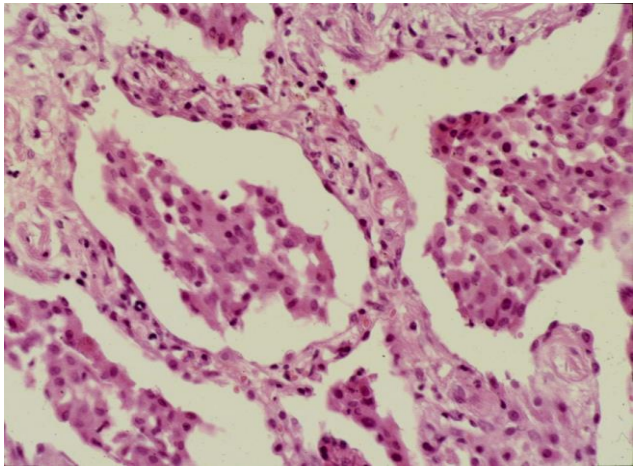
- Médicaments -> PnP classiques (NF)
- PR et autres maladies de système: Dg délicat
- Biothérapies - nouvelles molécules: IRAE
- Drogues illicites
- Substances disponibles *via* Internet
  - Tableaux graves, brûlures, traumatismes, bystanders
- Maladies de système d'origine médicamenteuse
  - Mimes de leur équivalent idiopathique

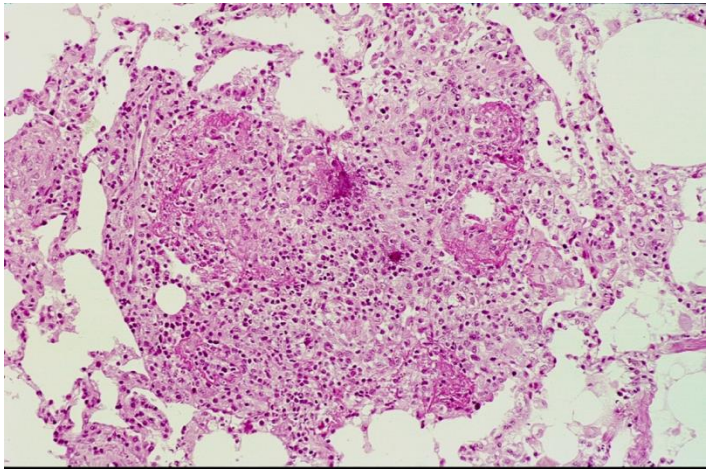
Pneumopathies subaiguës

- N: 250
- Nitrofurantoïne, methotrexate *I*-mTOR, azathioprine
- PINS-c ou granulomateuse
- Réversibles
- [*P jiroveci*]









Salehi *et al. Journal of Medical Case Reports* (2017) 11:174
DOI 10.1186/s13256-017-1333-0

Journal of
Medical Case Reports

CASE REPORT Open Access

Methotrexate-induced Hypersensitivity Pneumonitis appearing after 30 years of use: a case report

Mashal Salehi[1,2*], Robertha Miller[1,2] and Myint Khaing[1,2]

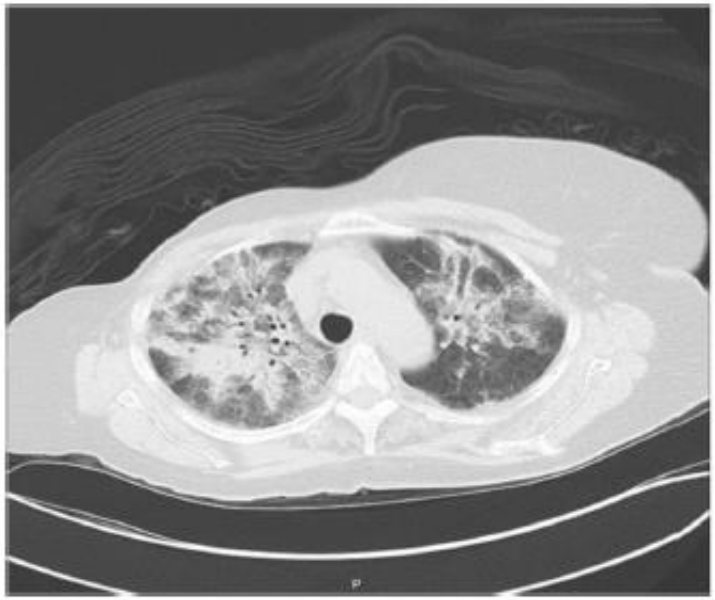


Fig. 2 Patient's chest computed tomography on admission

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

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.

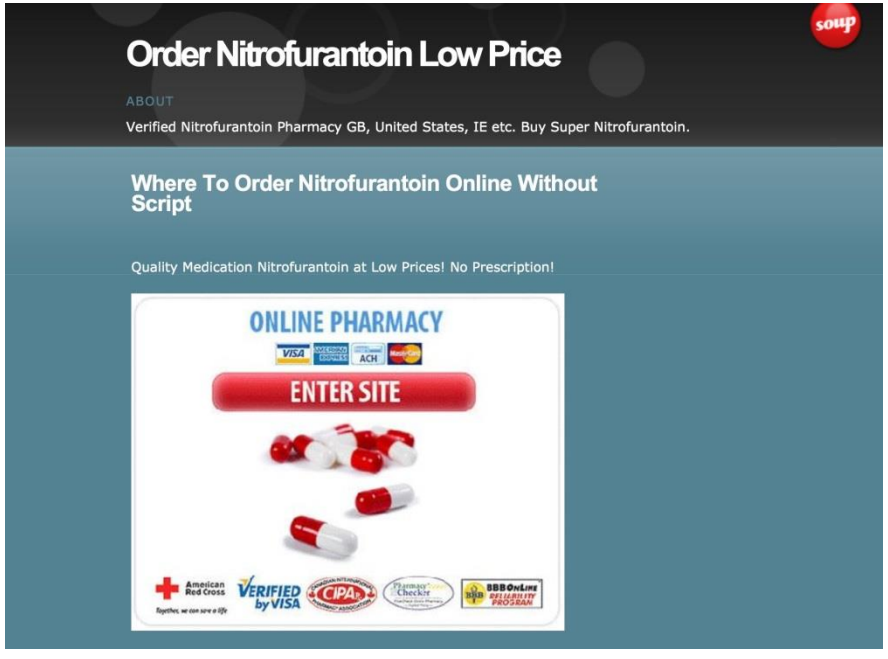
Competing interests: None declared.

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

Fast Delivery to UK, United States, NO and Worldwide!

Enter Here to order generic NITROFURANTOIN in our approved drugstore =>



CASE REPORT

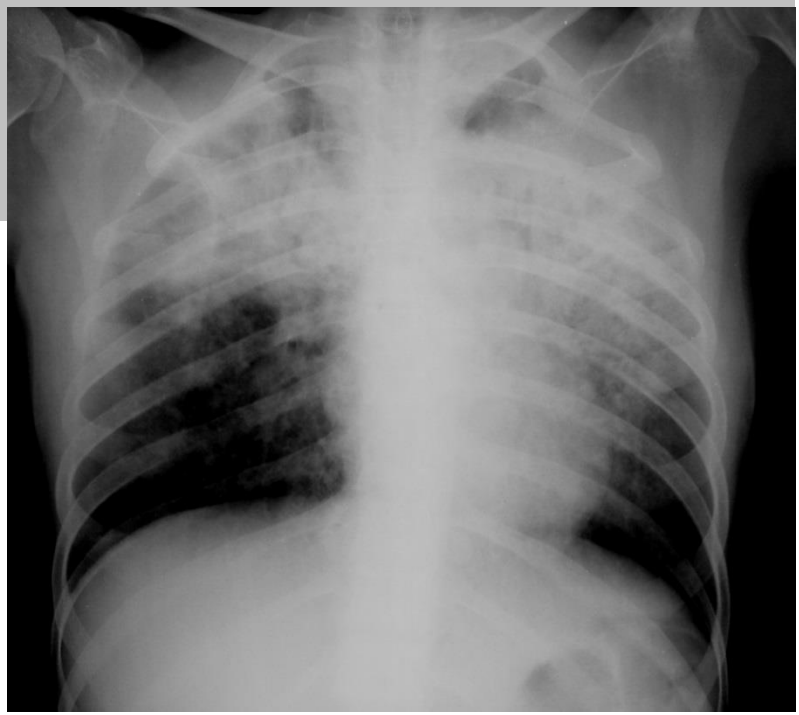
Fatal Nitrofurantoin Lung

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.

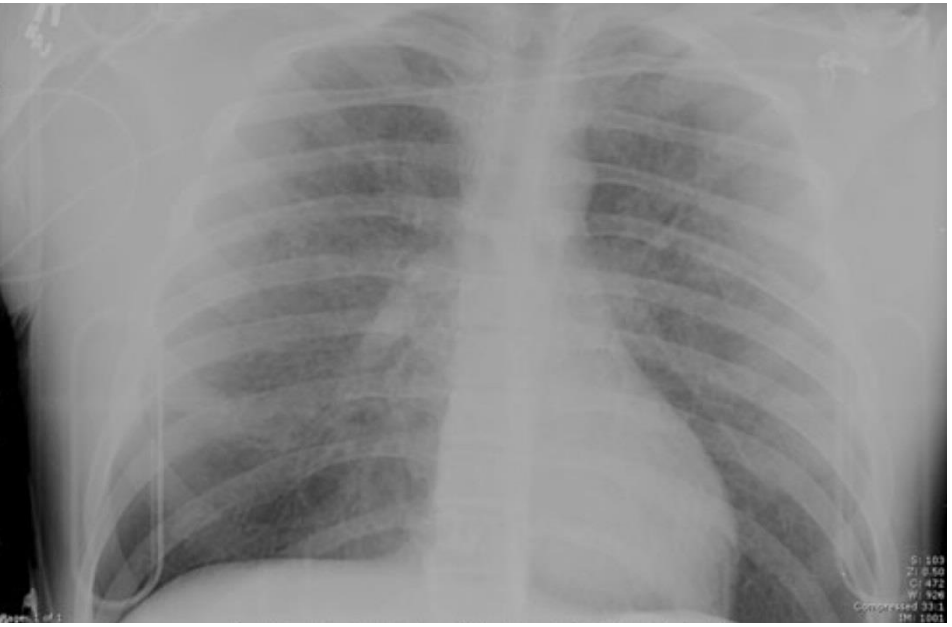
PnP (sur)-aiguës SDRA

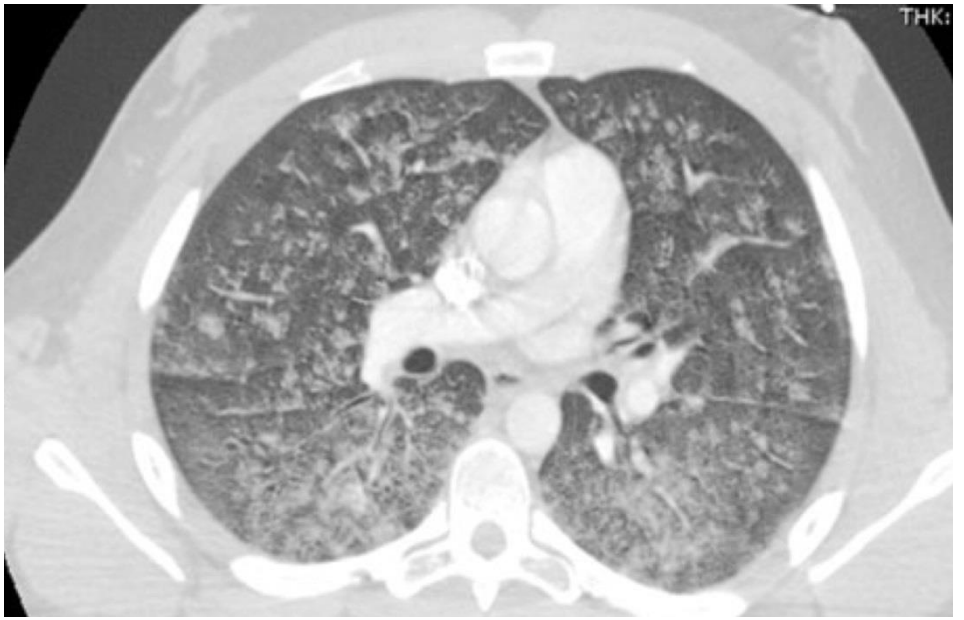


- N: 110
- Methotrexate, I-mTOR (chryso)
- LBA lymphocytaire
- NSIP-c dense
  - +- Œdème pulmonaire / DAD
- Corticothérapie souvent requise
  - Orale
  - Parentérale
  - Bolus ?

High Times, Low Sats: Diffuse Pulmonary Infiltrates Associated with Chronic Synthetic Cannabinoid Use

Sameir Alhadi · Anupama Tiwari · Rais Vohra · Roy Gerona · Janak Acharya · Kathryn Bilello





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)***

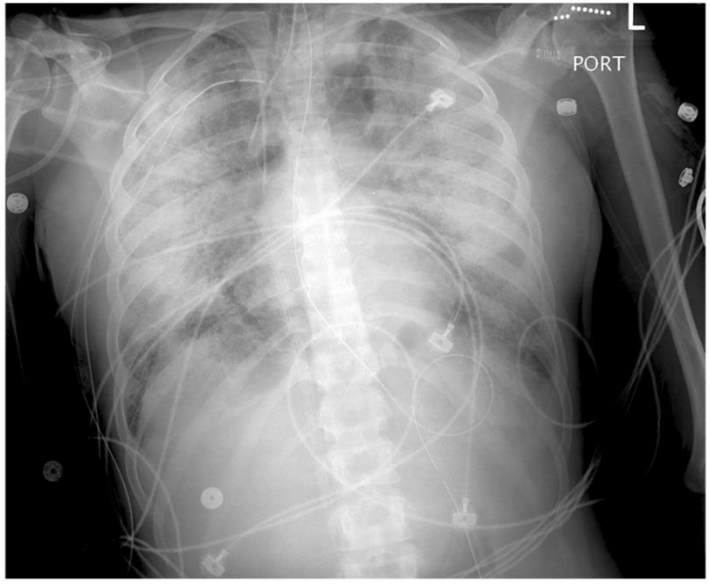


Fig. 1 *Patient 1. Chest radiograph at the time of ECMO cannulation shows diffuse pulmonary infiltrates bilaterally.*

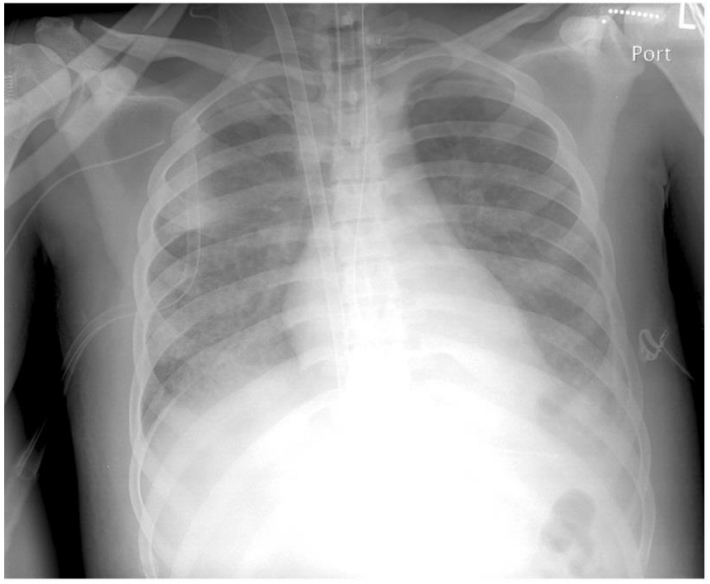


Fig. 2 *Patient 2. Chest radiograph at the time of ECMO cannulation shows diffuse pulmonary infiltrates bilaterally.*

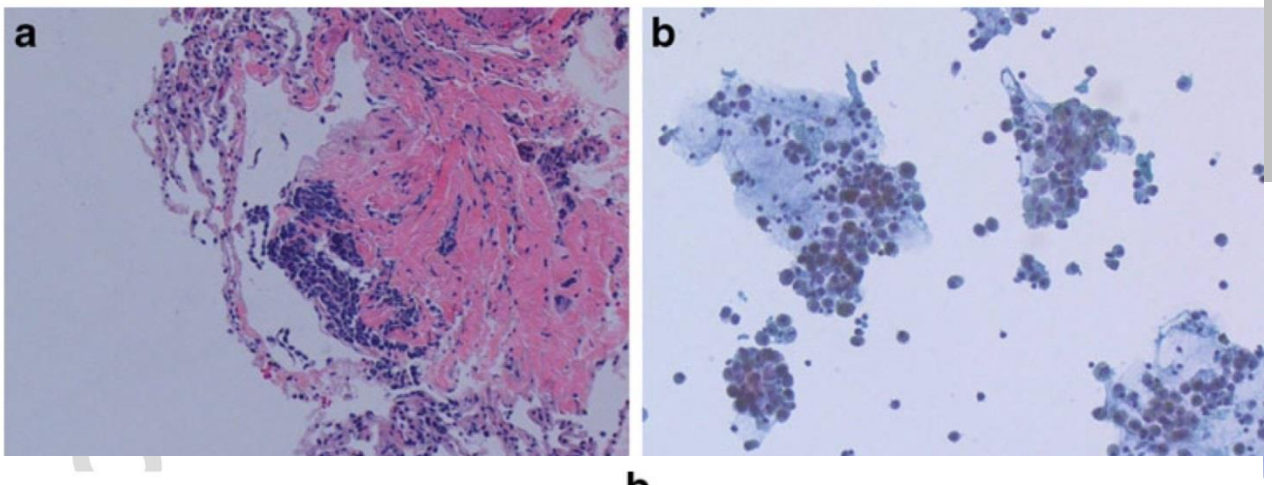


Fig. 6 **a** Hematoxylin and eosin stain at ×40 magnification of transbronchial lung biopsy, showing chronic inflammatory infiltrate in the lung parenchyma. **b** Broncho-alveolar lavage monolayer showing numerous macrophages with a refractile, non-ferric brown pigment. (×40)

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"

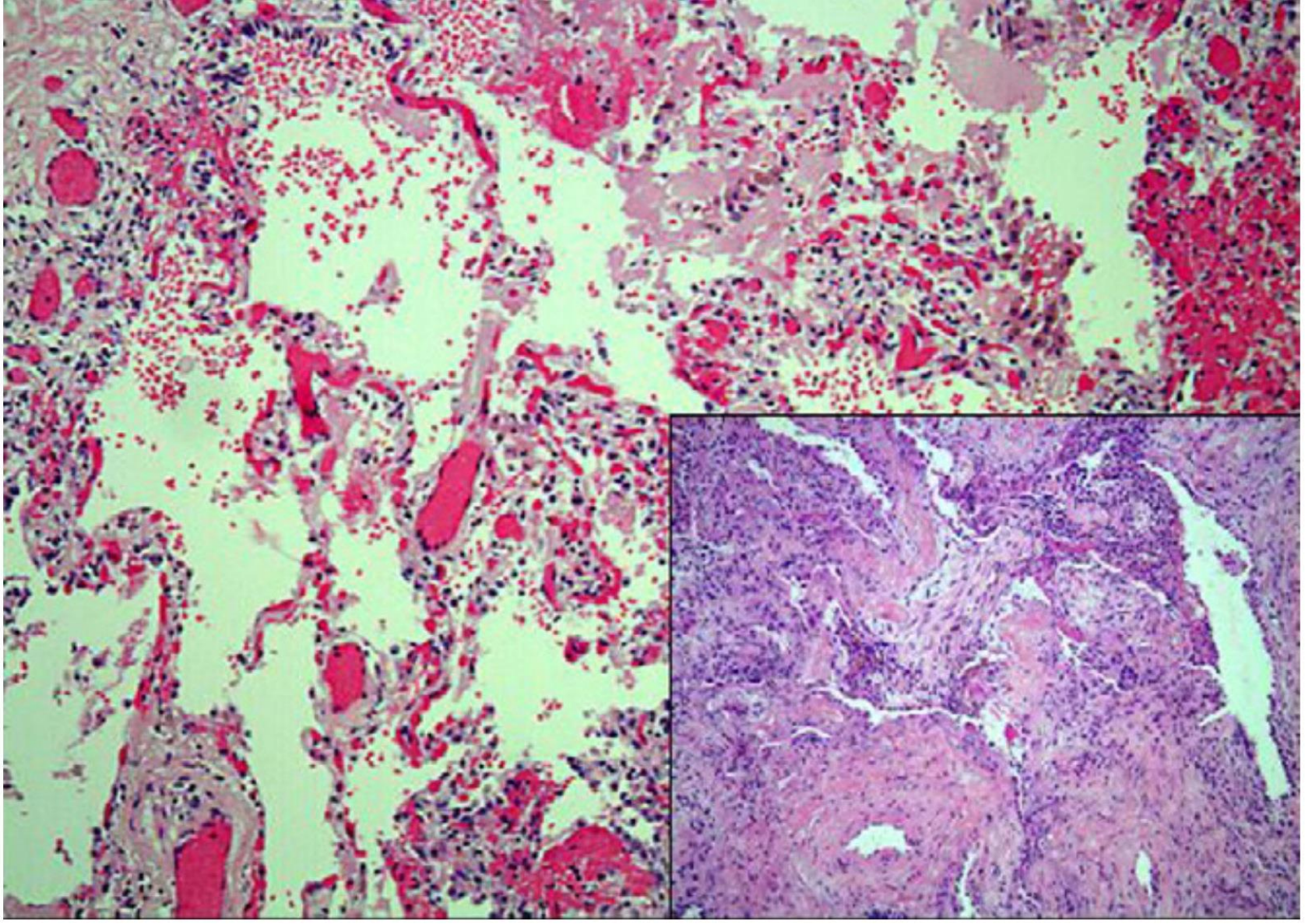
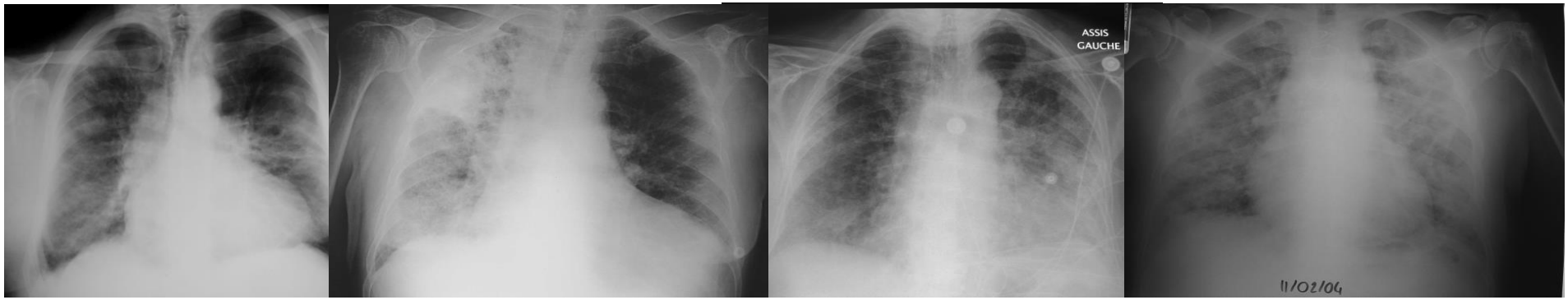
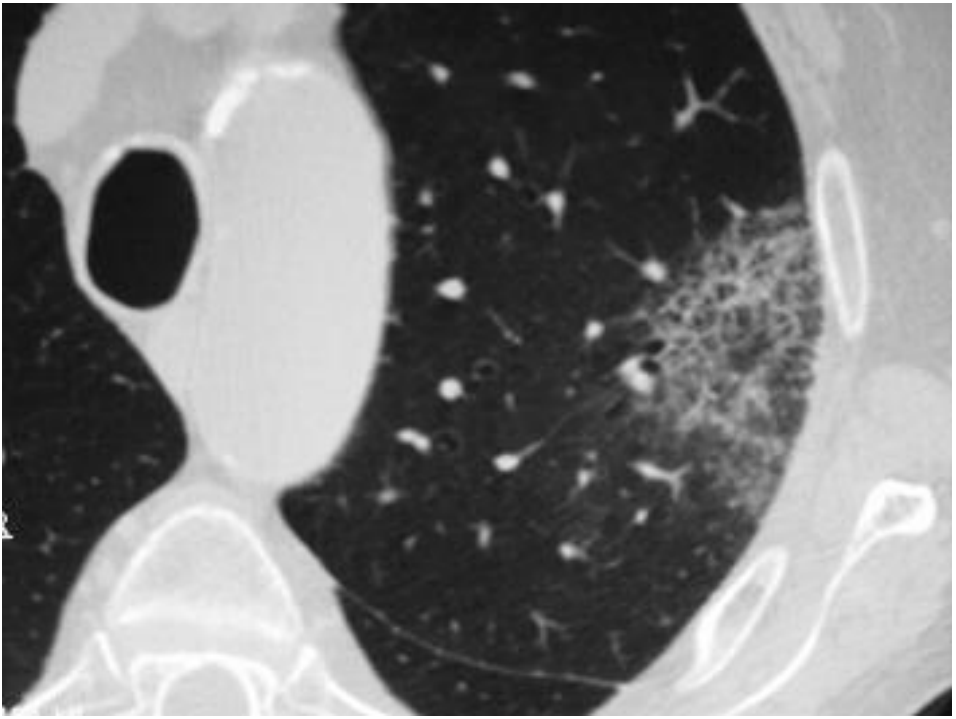


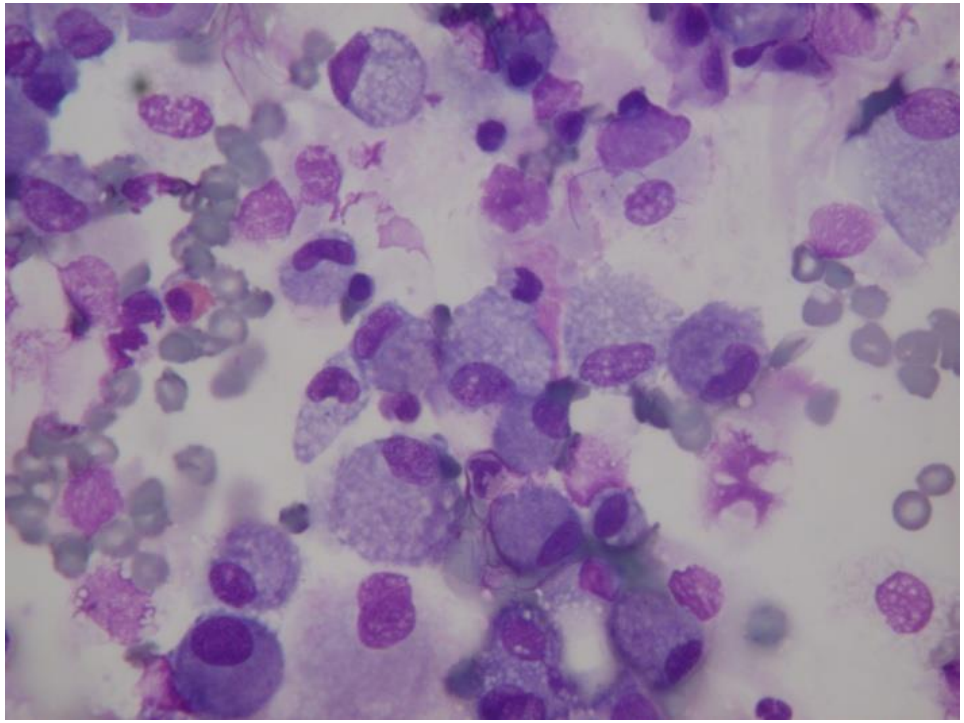
Fig. 2. Diffuse alveolar damage (DAD): interstitial and alveolar oedema and/or fibroblastic proliferation in association with epithelial and endothelial damage and alveolar fibrin laminar accumulation in the form of hyaline membranes.

Amiodarone

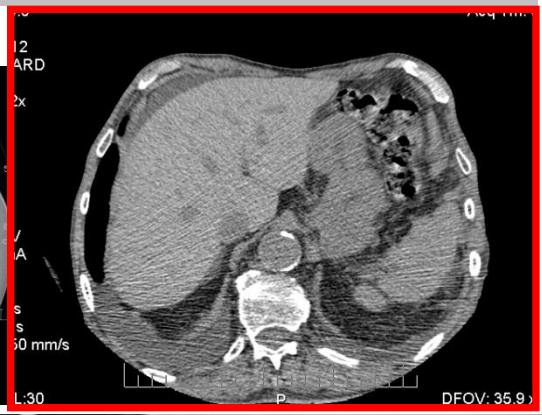
- 977 articles
- 6-12 mo (150-180 g)
- [Qq jours (post-op), 14 ans]
- Insidieux (semaines-mois)
- Dyspnée, toux, fébricule, doul. Pleurétiques, ‘cyanose’
- Présentations variées

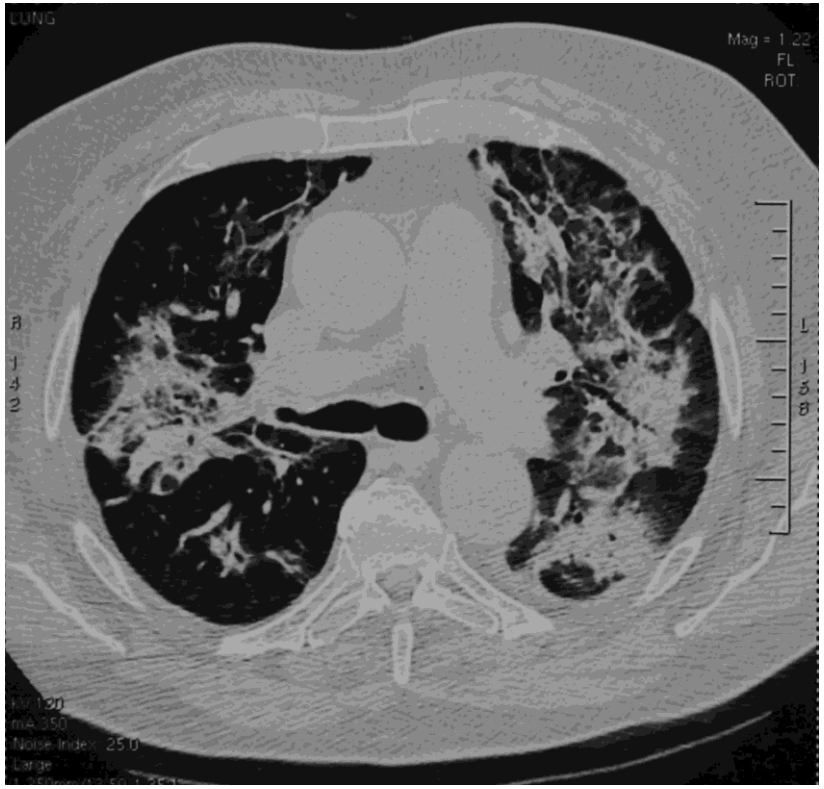




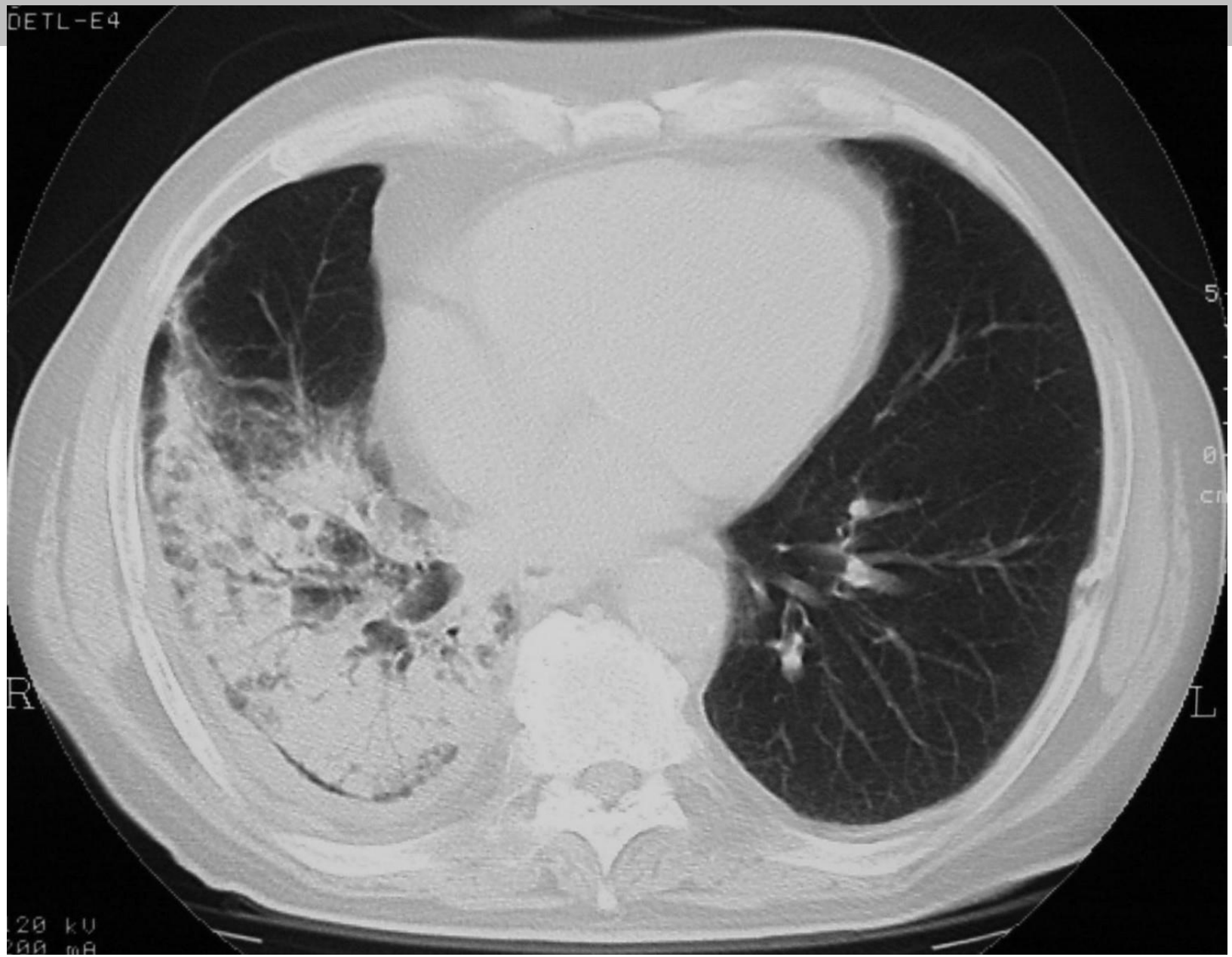


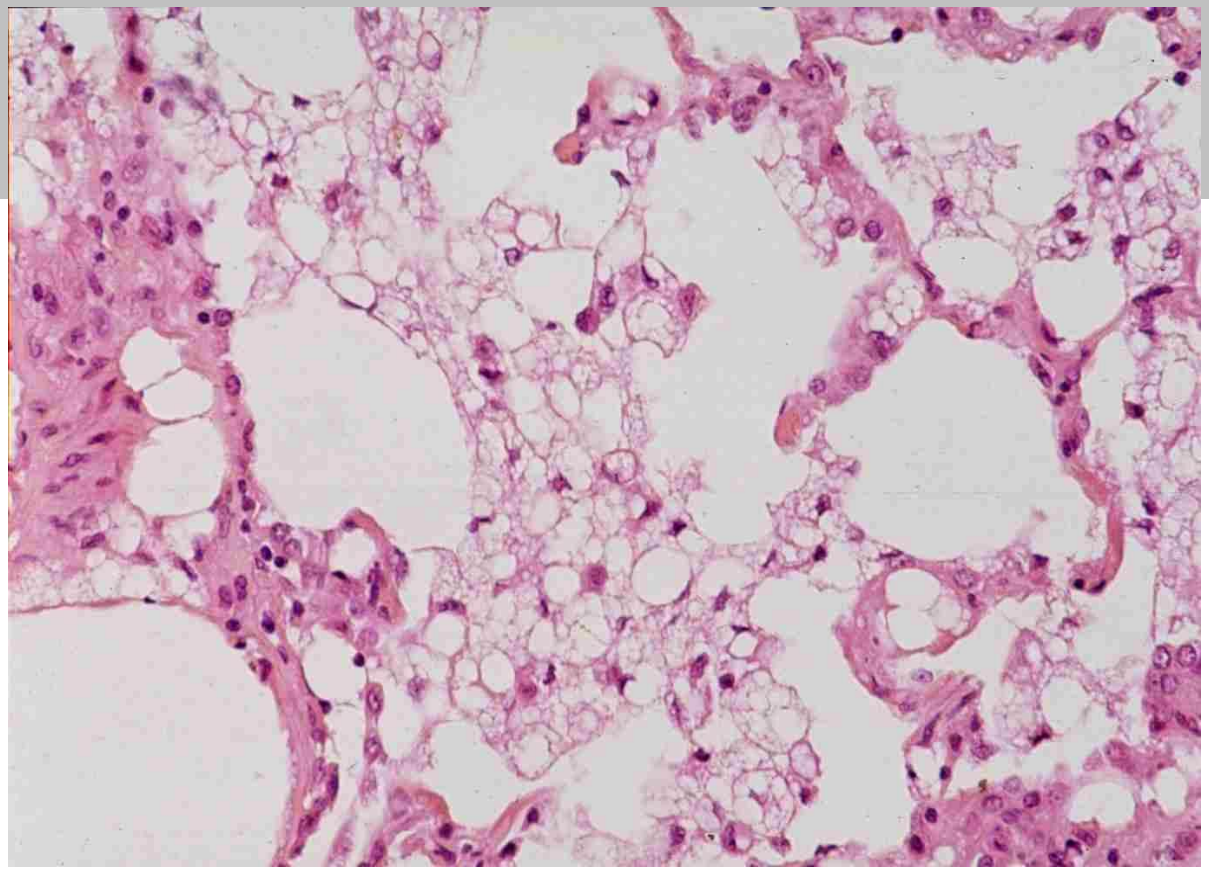

512 x 512
STANDARD
120.0 kV
154.0 mA
1.3 mm
Tilt: 0.0
ET: 0.7 s
GP: 0.0 s
TS: 0.00 mm/s

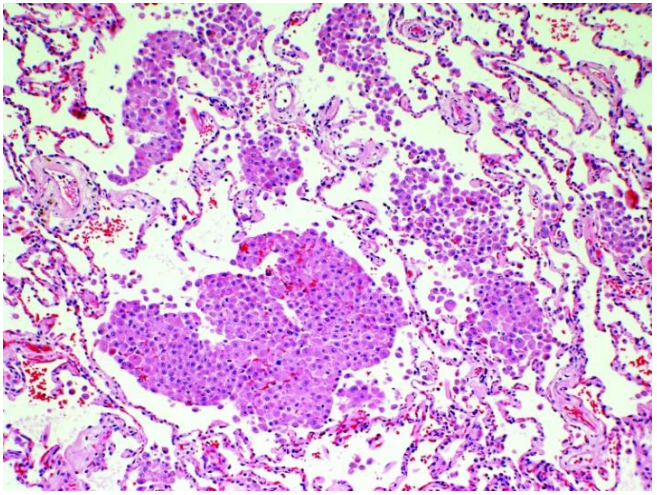

DFOV: 35.9

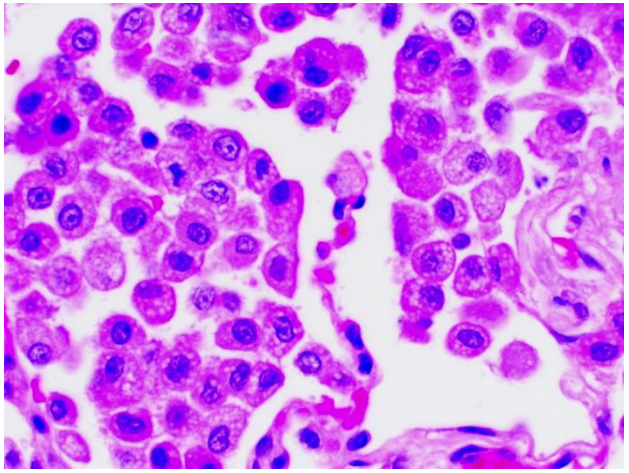

Mag = 1.22
FL
ROT

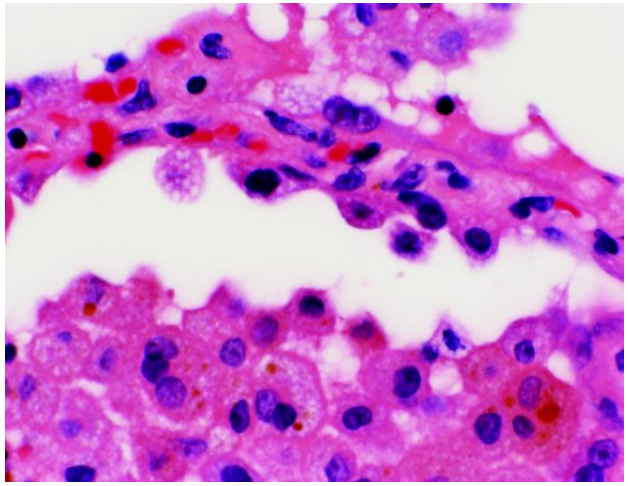

kV 120
eff.mAs 88


DETL-E4
R
L





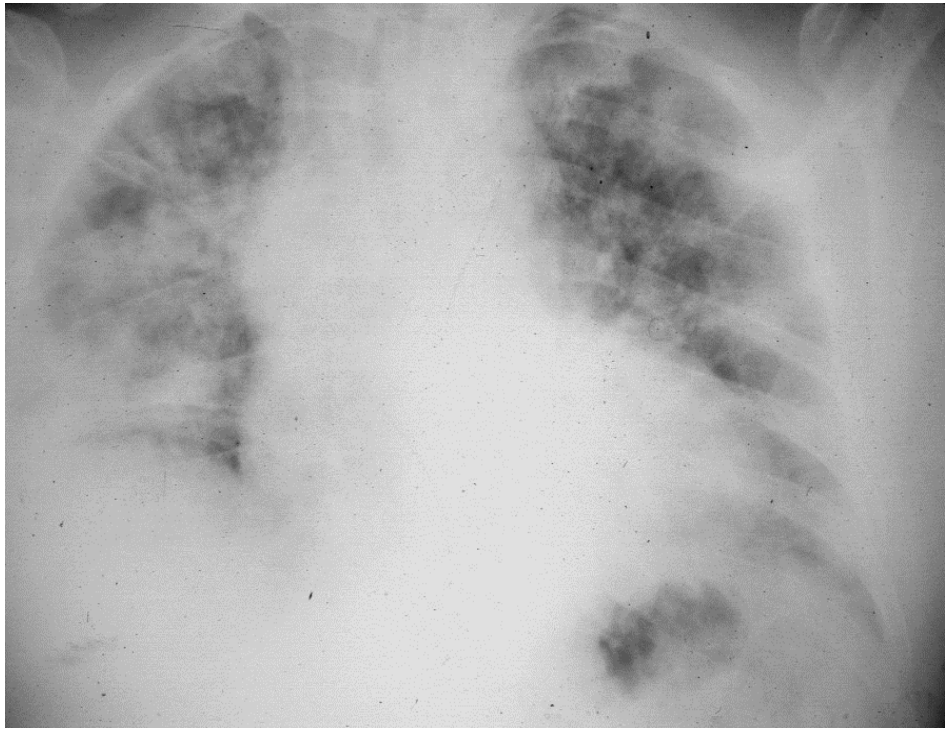


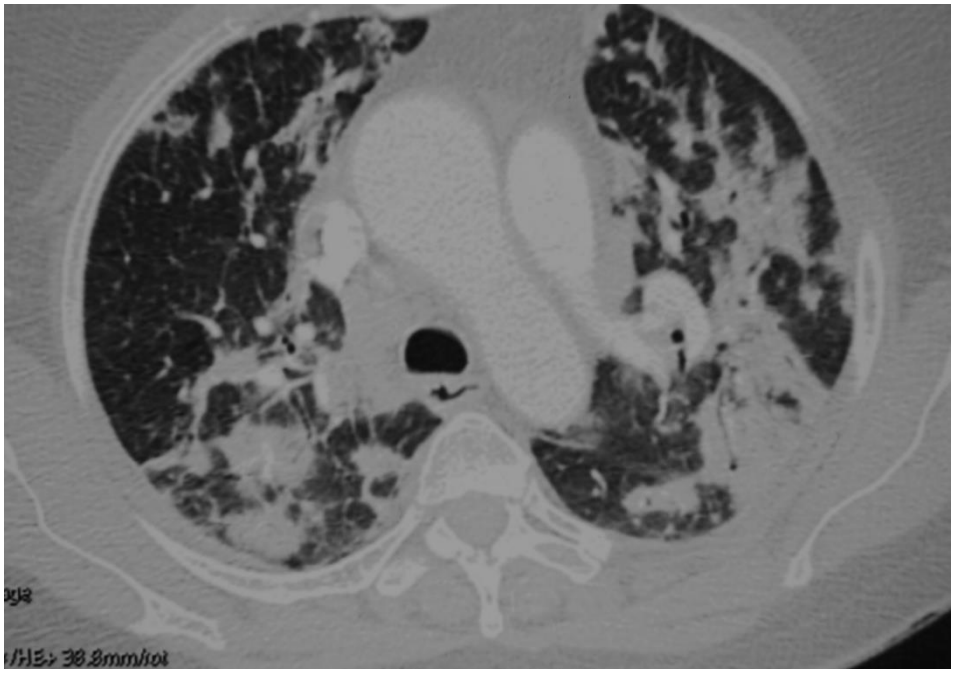


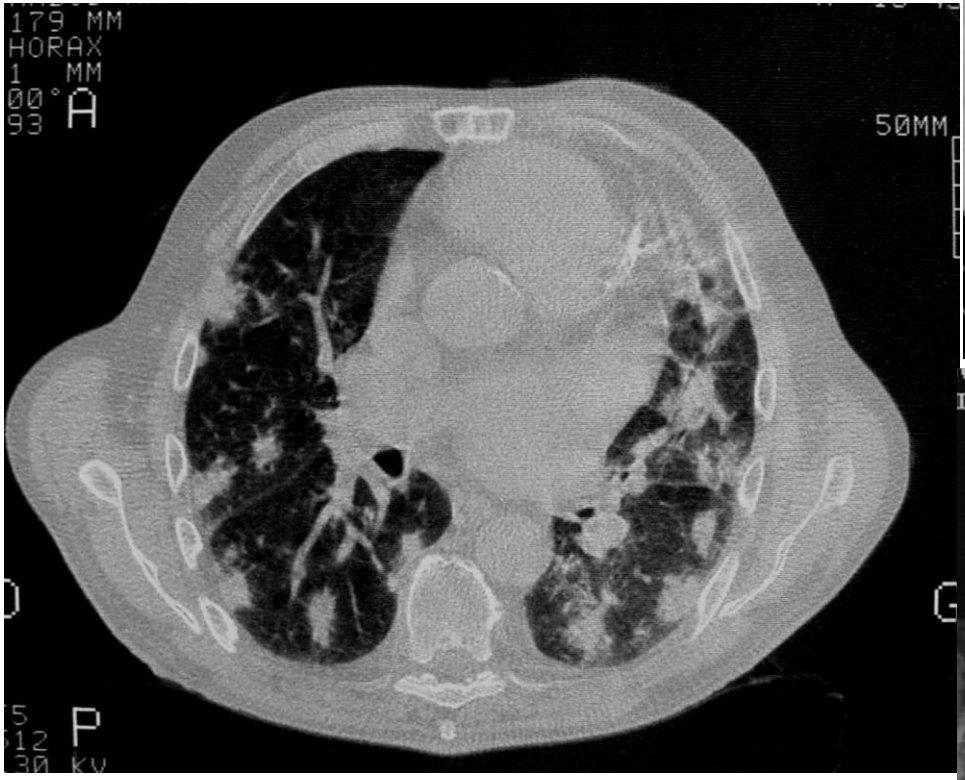
SDRA

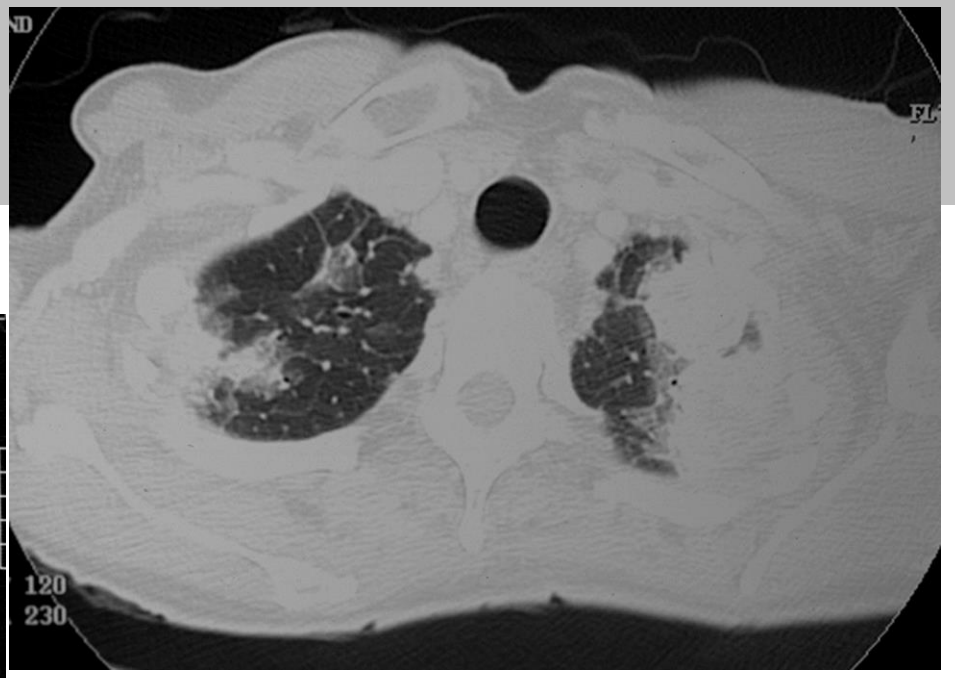

Né(e) le : 30-08-1918
2083 PNEUMOLOGIE UO HOSPITALI
Examen du 01-03-2002

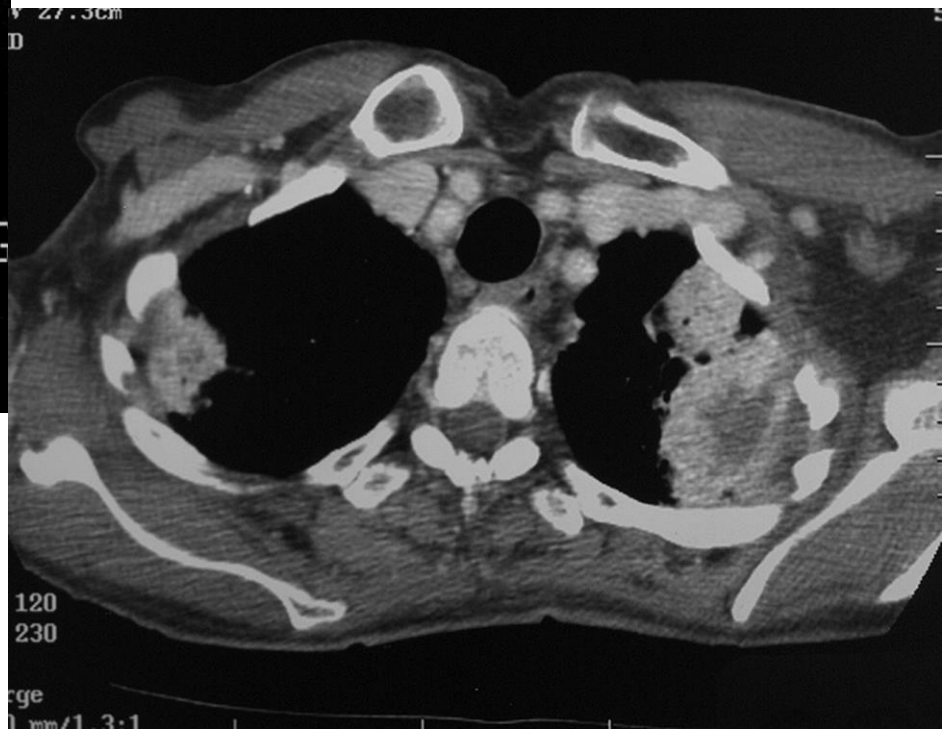
Formes atypiques

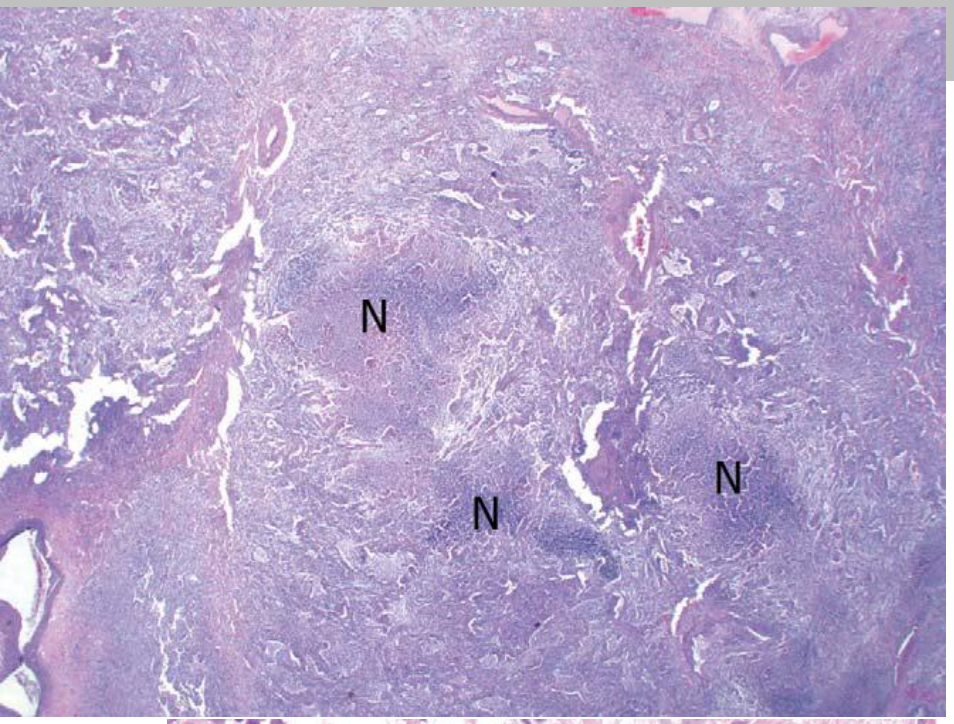


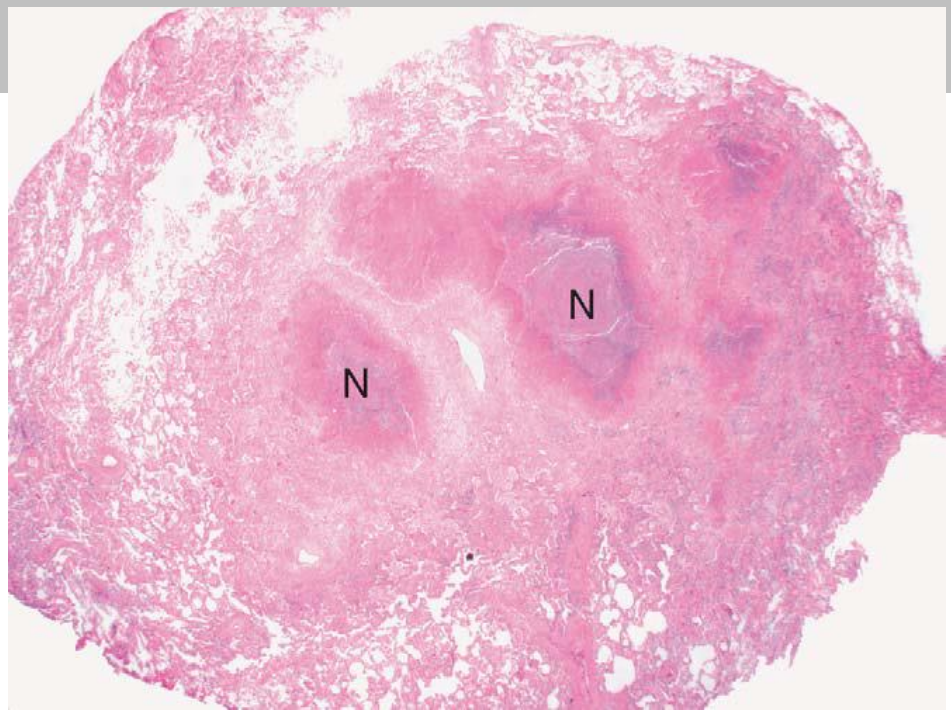


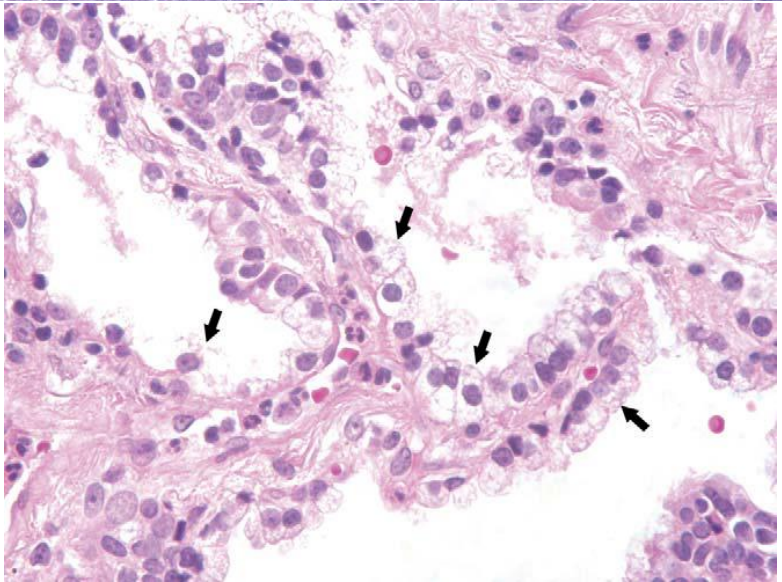

179 MM
HORAX
1 MM
00°A
93
50MM
P

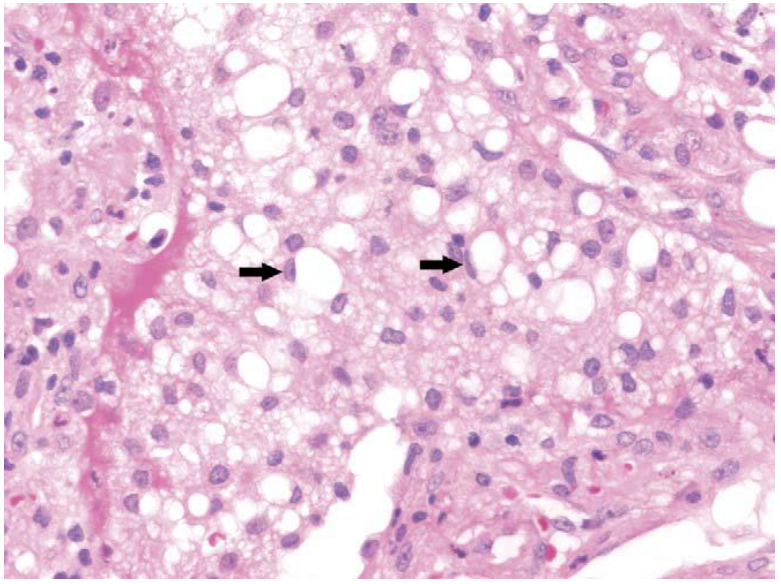

ND
FL
120
230


27.3cm
D
120
230


N
N
N

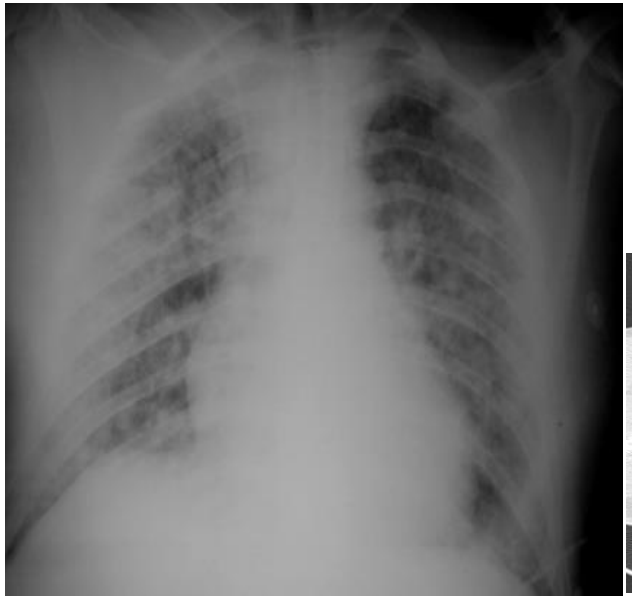

N
N

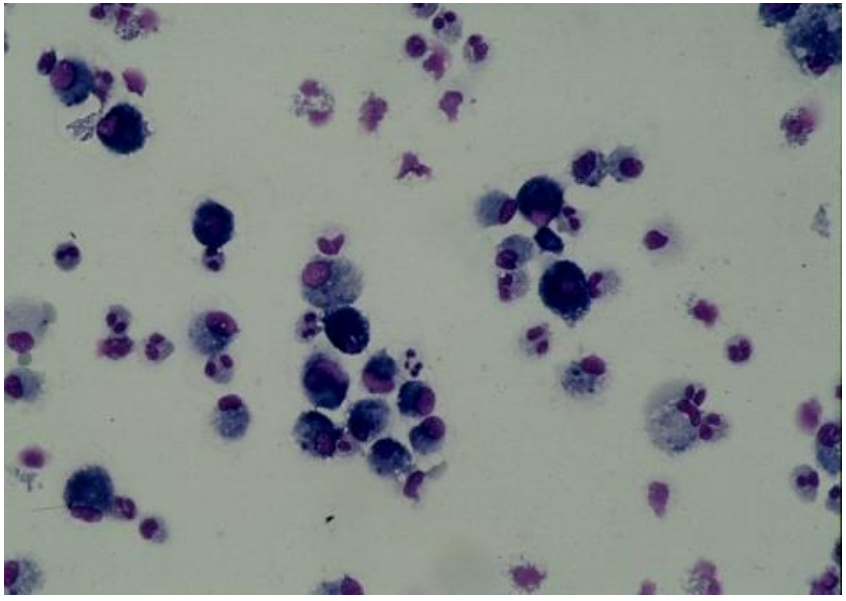


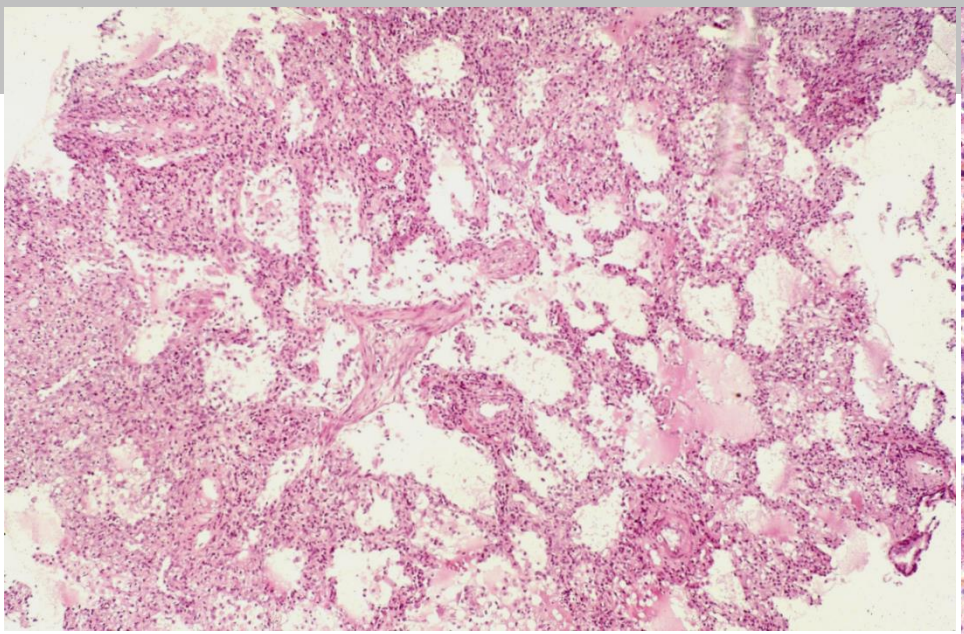
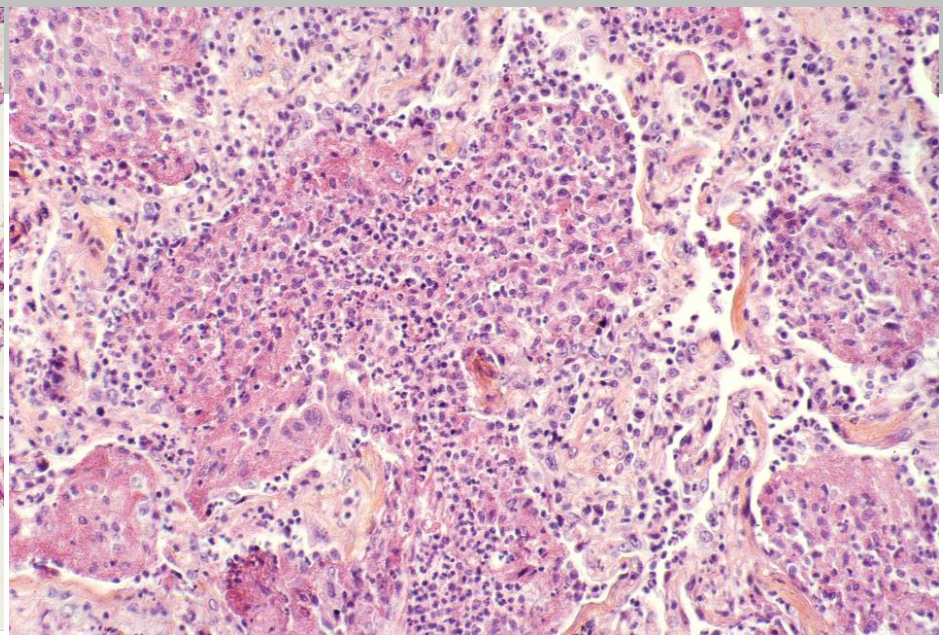


Eosinophilies pulmonaires medicamenteuses

- n=170
- AINS, quinine, daptomycine minocycline tabac, cocaine
- Eosinophilie
  - NF, LBA, tissus

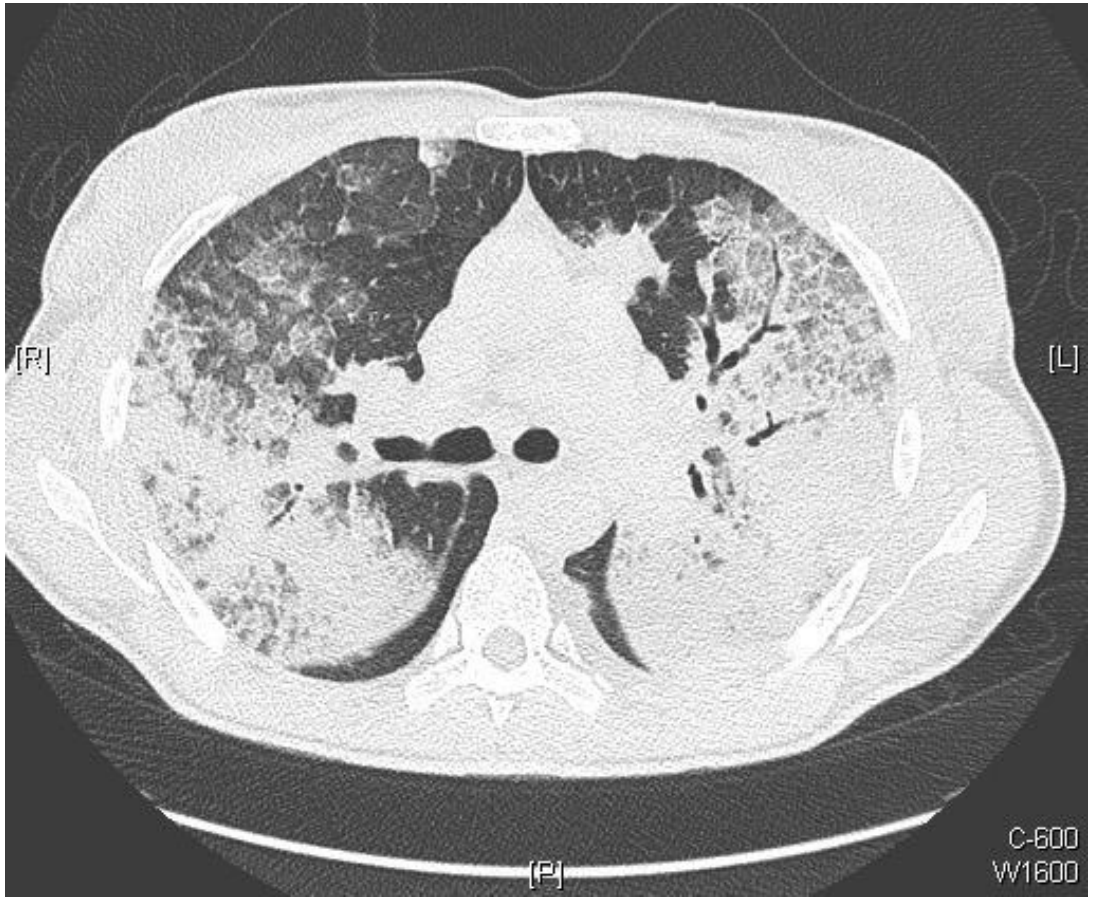


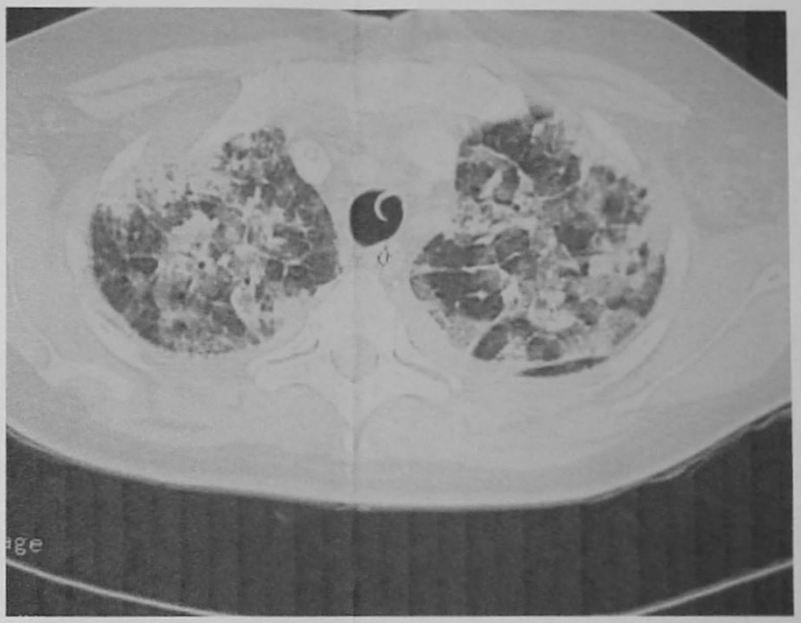


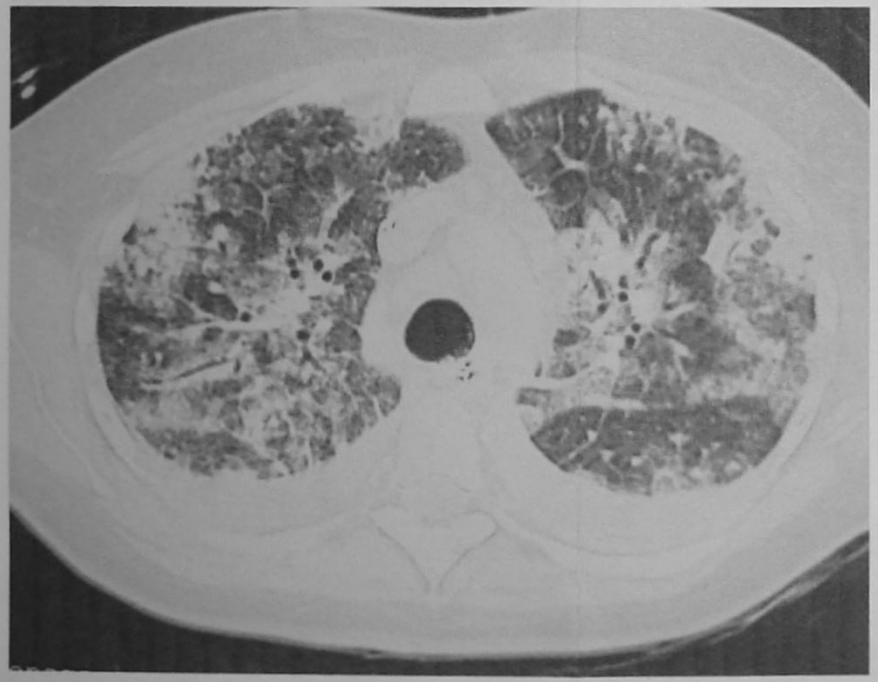



- Eviction
- Bilan d’éosinophilie (infestation parasitaire)
- Corticothérapie ±
- Réintroduction parfois possible

- Formes graves
  - PnP aiguë à ésosinophiles
  - DRESS
  - EGPA








Average

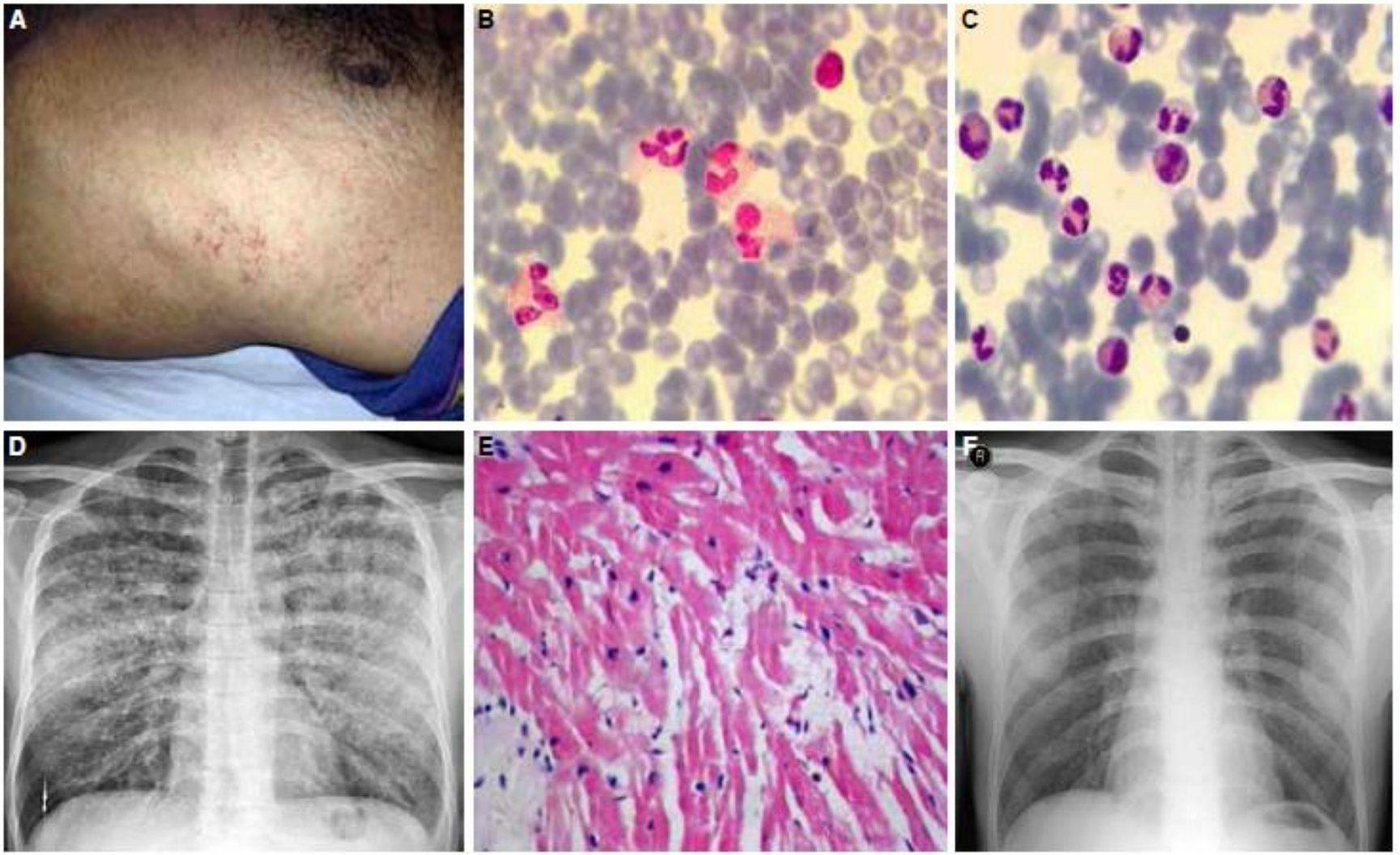
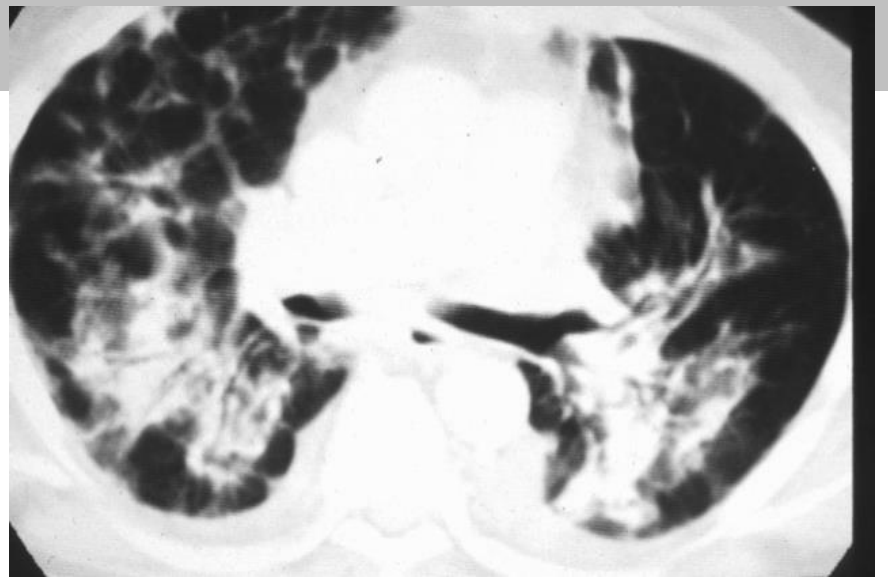
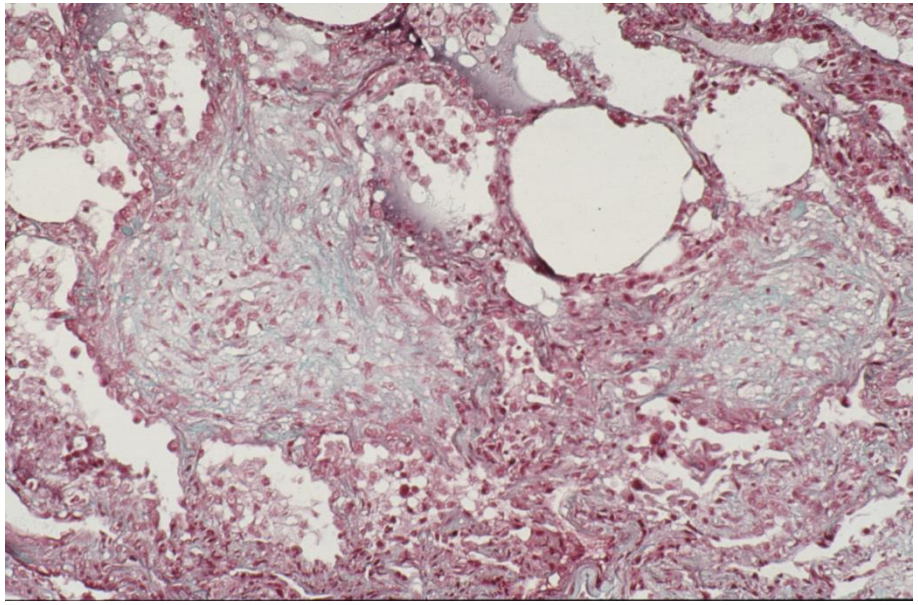


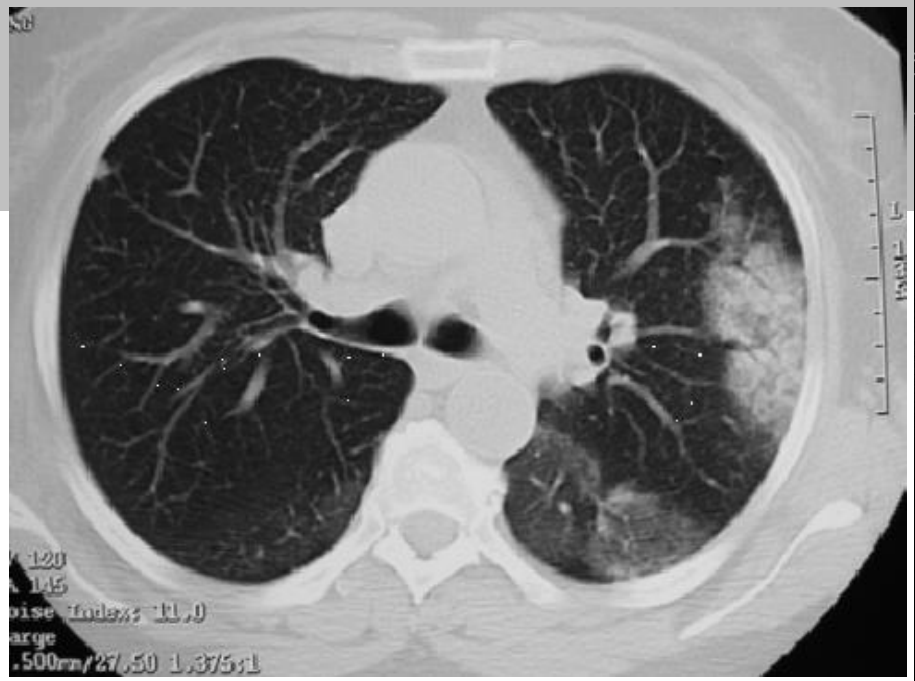
Figure 1. **(A)** Rash on the patient's chest. **(B)** Eosinophilia on peripheral blood smear. **(C)** Bone marrow aspiration and biopsy. **(D)** Chest x-ray demonstrating bilateral interstitial and reticulonodular infiltrates. **(E)** Pathologic specimen of endomyocardial biopsy. **(F)** Chest x-ray following treatment.

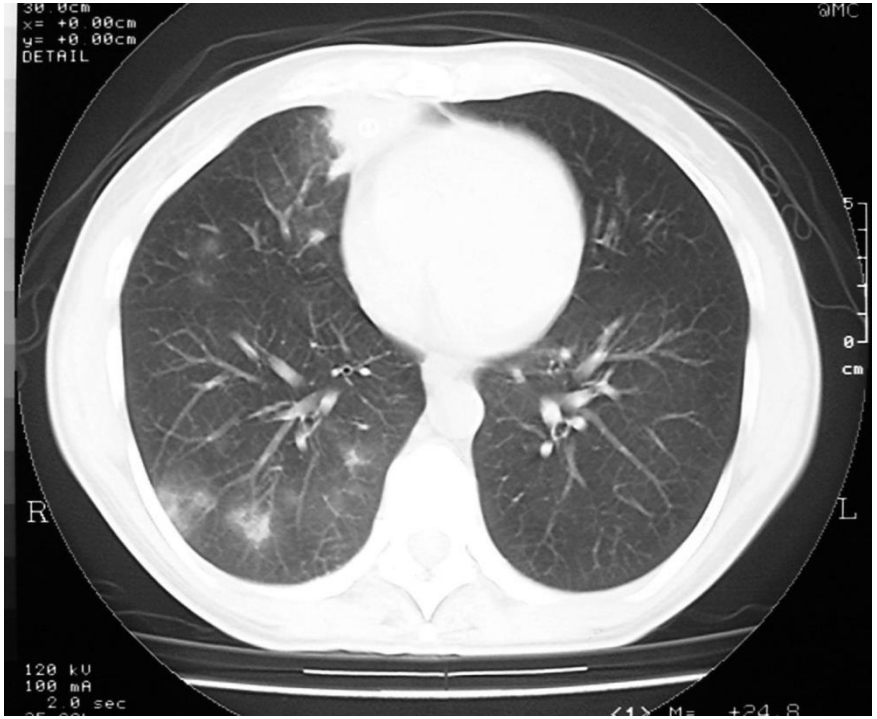
BOOP

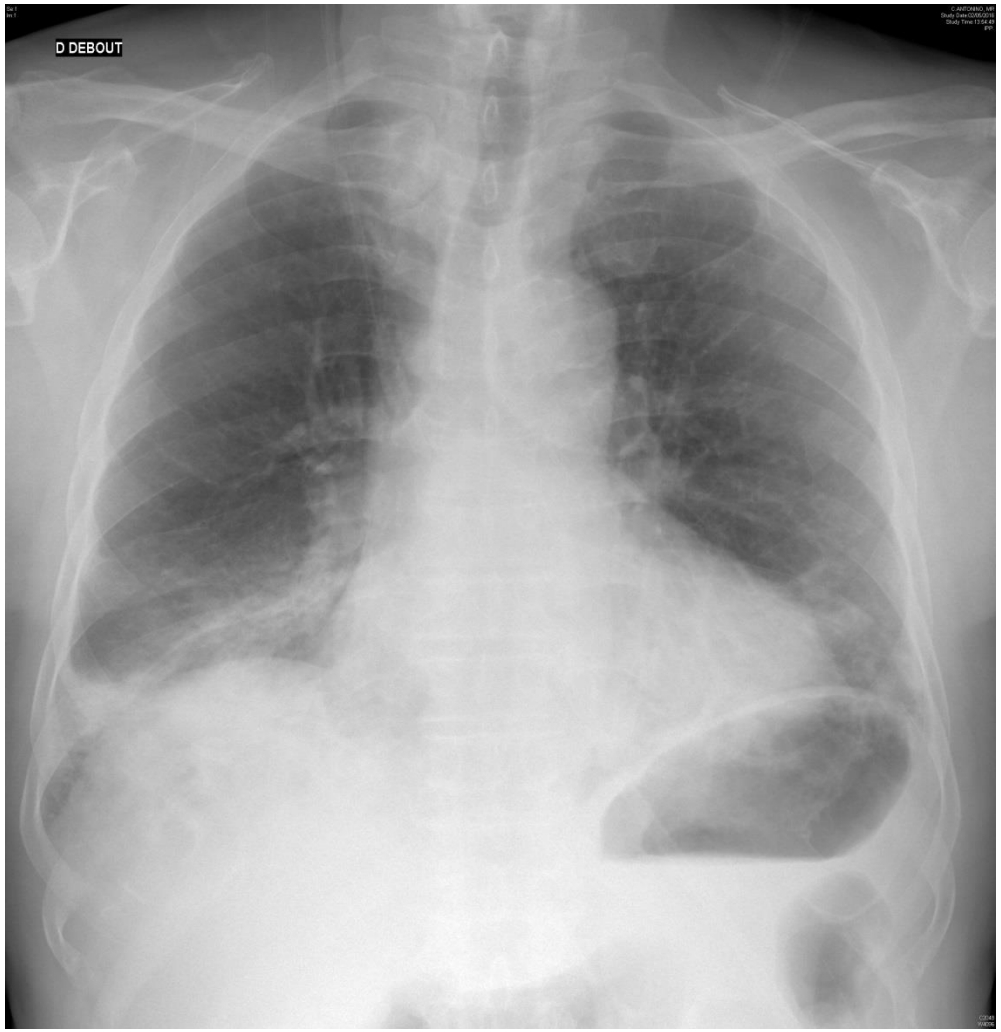
- N=100
- Amiodarone, statines bleomycine, nitrofurantoine rituximab, FOLFOX…
- Présentations
  - Foyers migrants
  - Masse(s)
  - SDRA
- BOOP *sine* pathology
- Eviction
- Corticothérapie +-

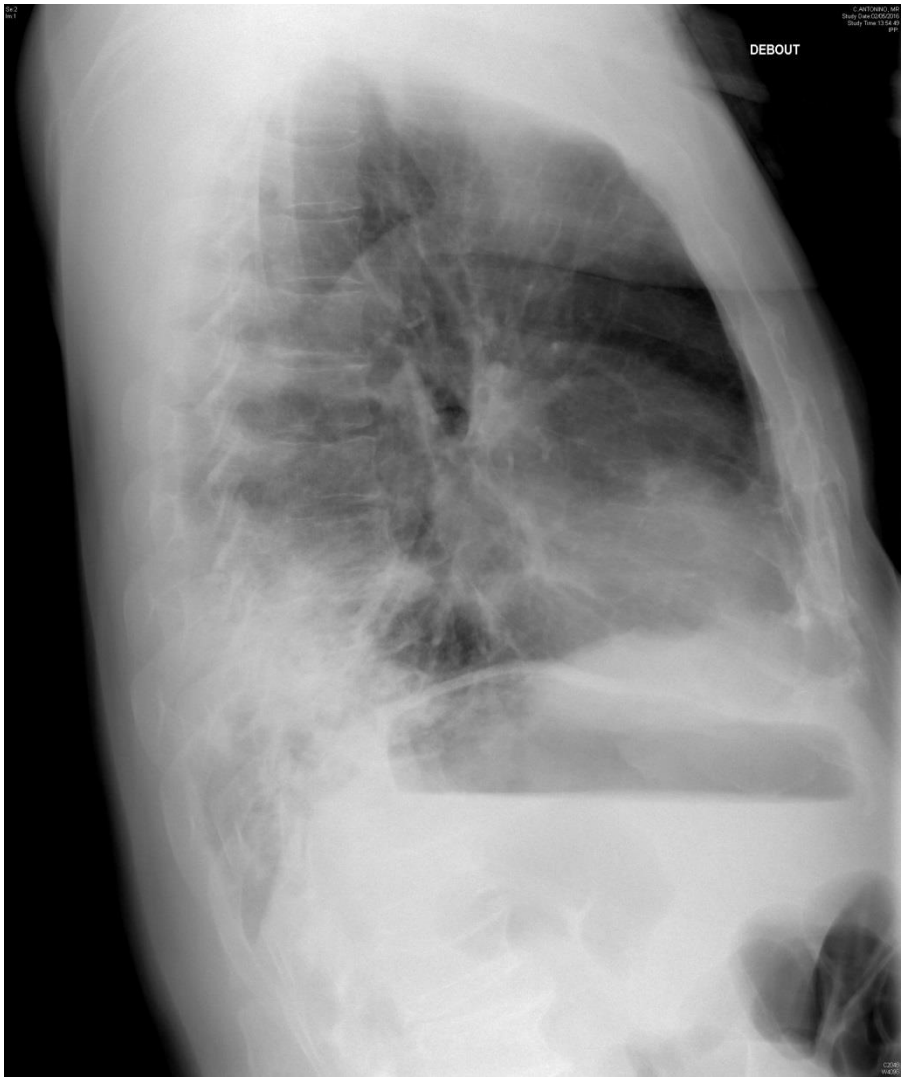







x= +0 00cm
y= +0 00cm
DETAIL
R
L
120 kV
100 mA
2.0 sec


D DEBOUT


DEBOUT

AFOP

- Amiodarone
- Statines
- FOLFOX

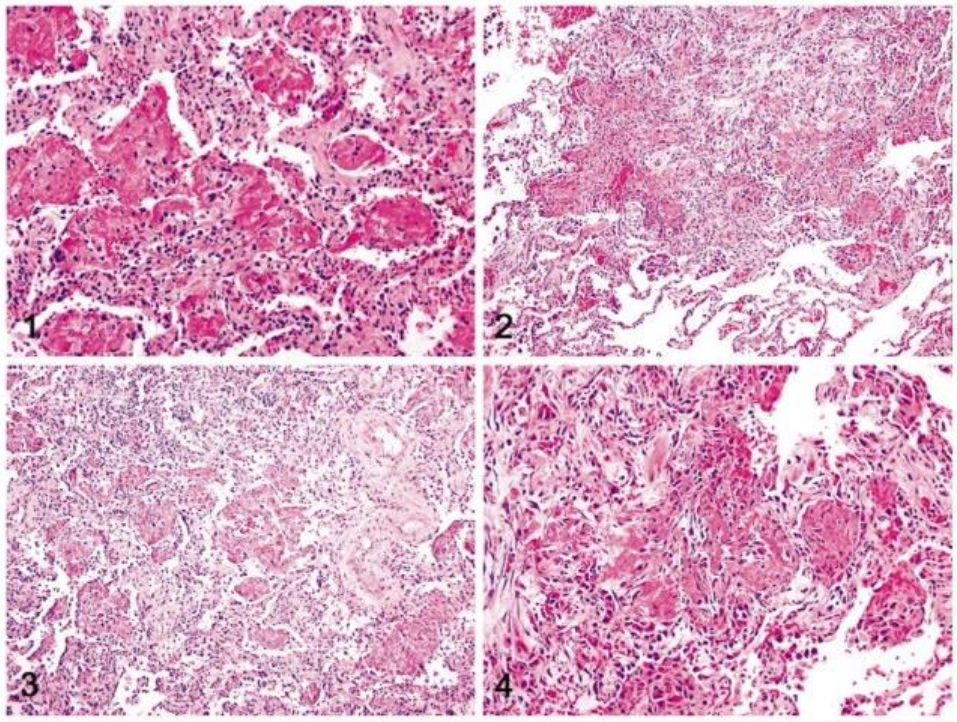
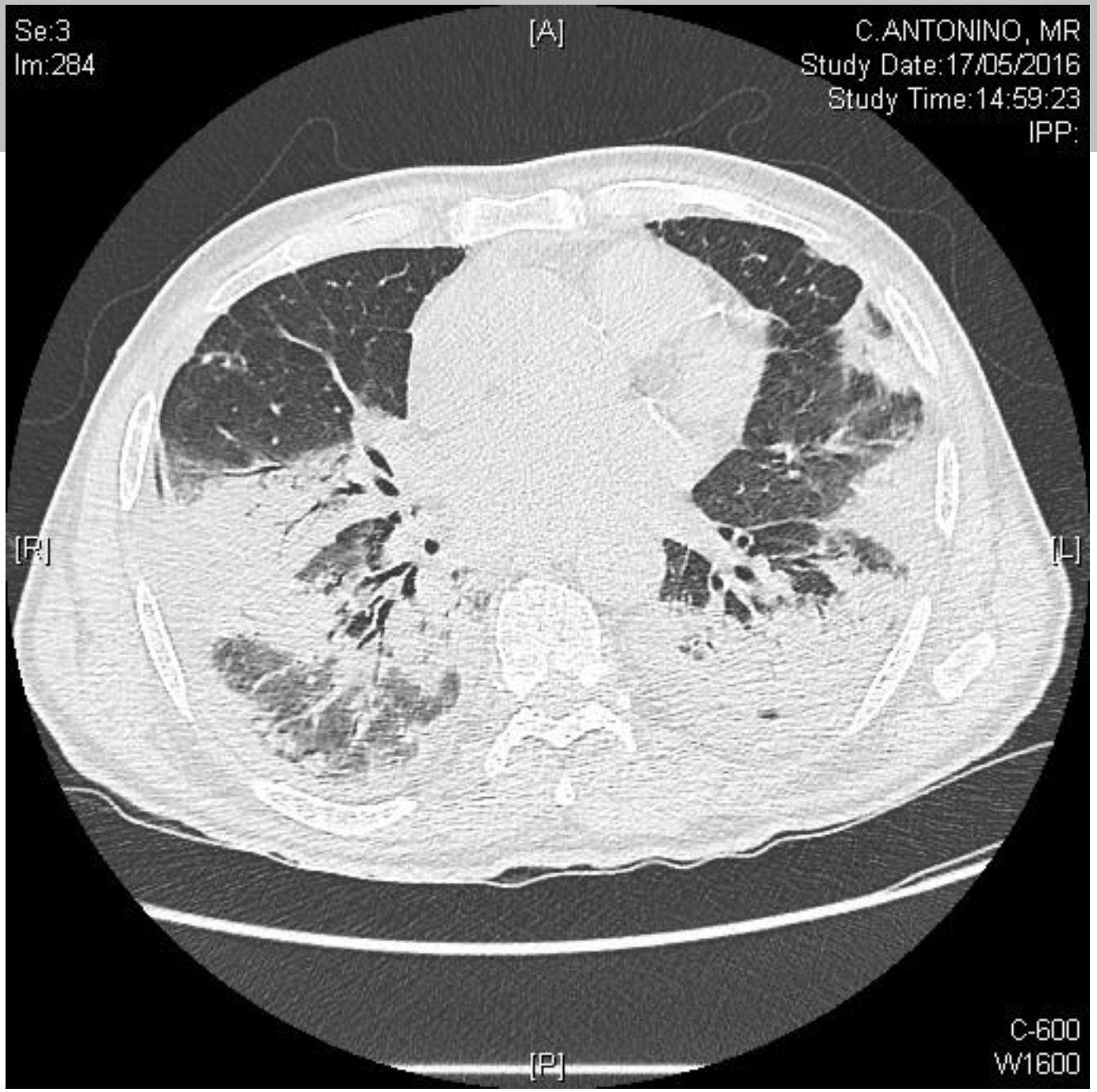


Figure 1. *Intra-alveolar fibrin in the form of "fibrin balls" without formation of hyaline membranes (hematoxylin-eosin, original magnification ×160).*


Se:3
Im:284
[A]
C.ANTONINO, MR
Study Date:17/05/2016
Study Time:14:59:23
IPP:
[R]
[L]
[P]
C-600
W1600

Fibrose pulmonaire médicamenteuse…

- N=80 médicaments sités
- ‘Fibrose’ dans le titre ou les mots-clés: 954 papiers
- Histologie confirmative: 104

JCP Online First, published on April 27, 2013 as 10.1136/jclinpath-2012-201338

Smoking-related interstitial fibrosis (SRIF): pathologic findings and distinction from other chronic fibrosing lung diseases

Anna-Luise A Katzenstein

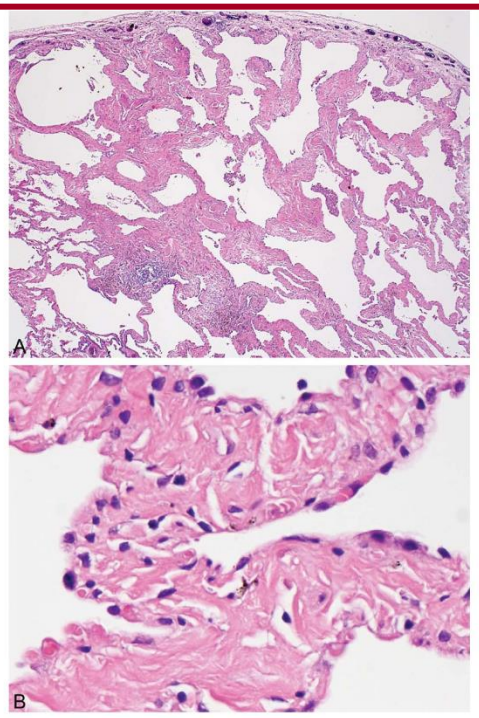


Figure 1 (A) Low magnification view of smoking-related interstitial fibrosis (SRIF) showing the characteristic marked thickening of alveolar septa in subpleural parenchyma associated with emphysema. Clusters of pigmented macrophages indicative of RB are present in some airspaces. The pleural surface is on the top. (B) High magnification view of same case showing the thick, ropey, hyalinised collagen deposition within alveolar septa typical of SRIF.

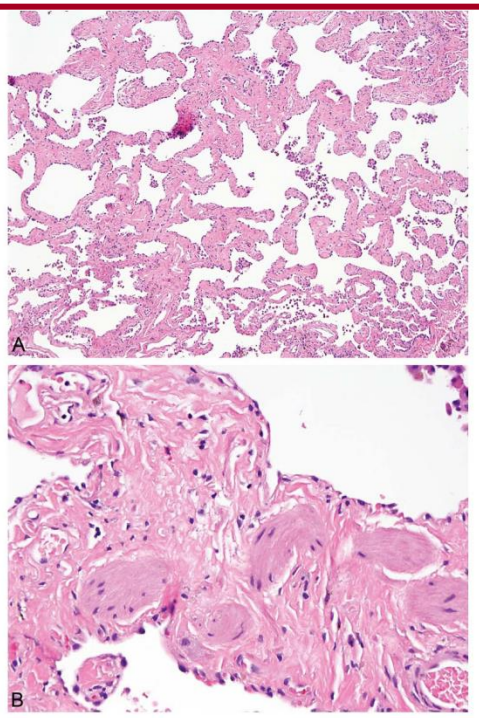


Figure 2 (A) Low magnification view of smoking-related interstitial fibrosis within deeper lung parenchyma. (B) Higher magnification showing typical eosinophilic collagen deposition along with entrapped, hyperplastic smooth muscle bundles.

appearance of the fibrosis, the amount of accompanying inflam-

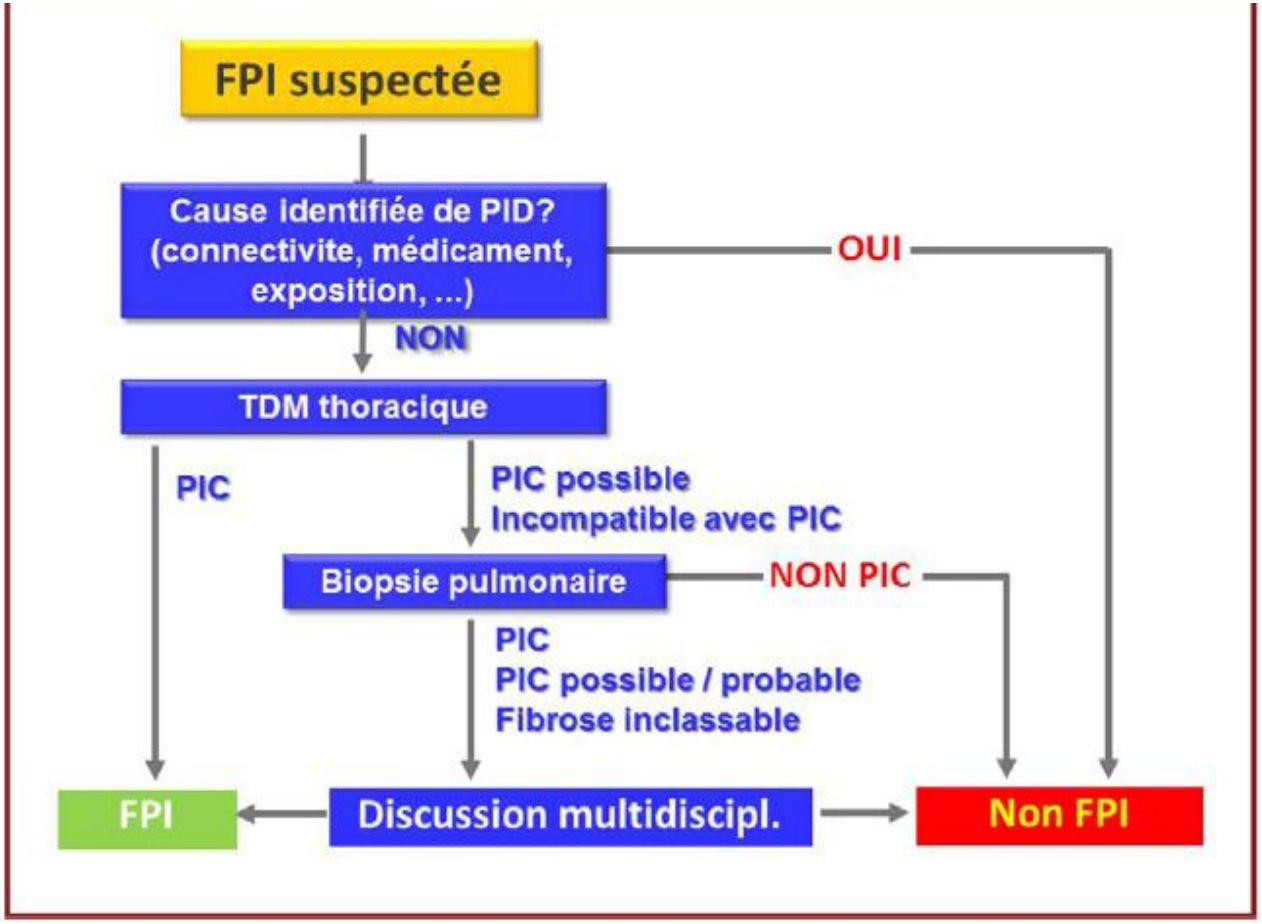
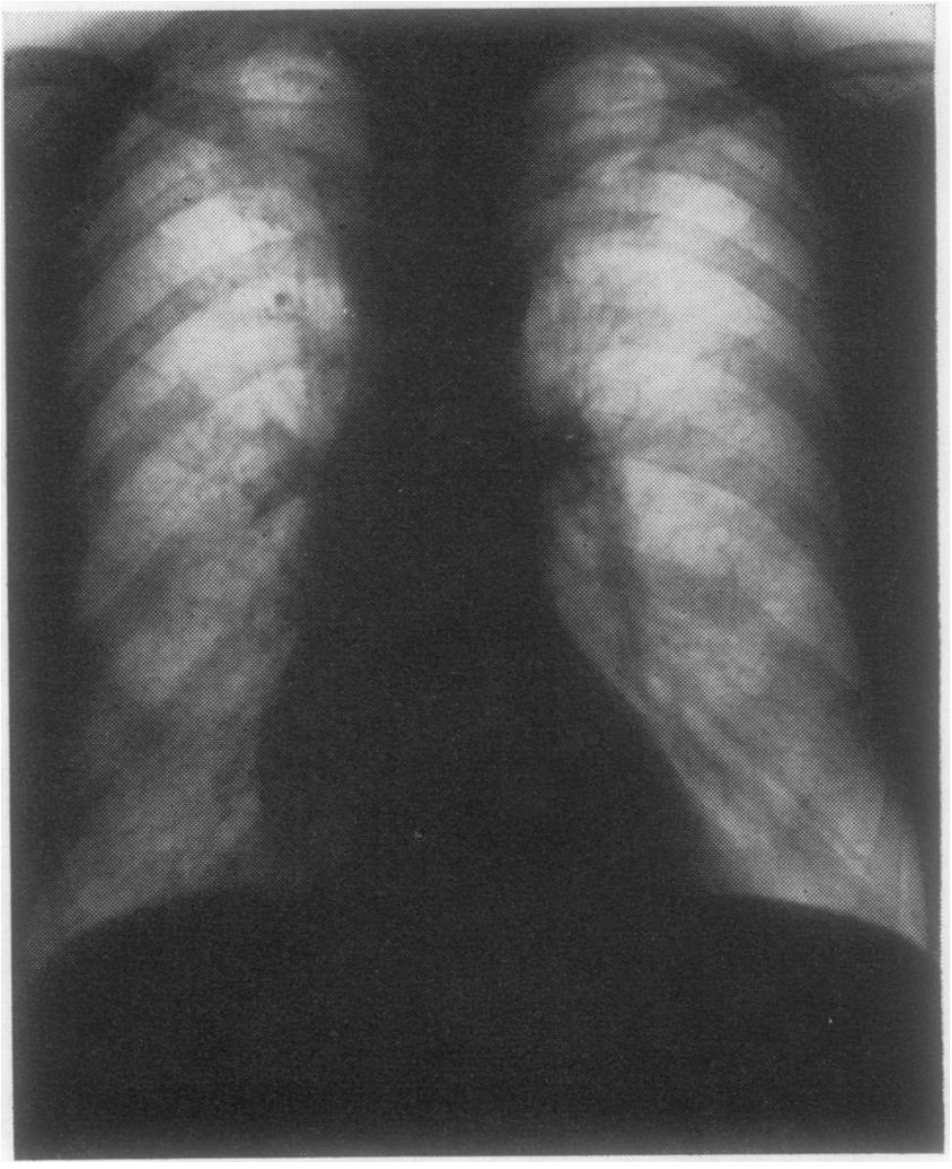
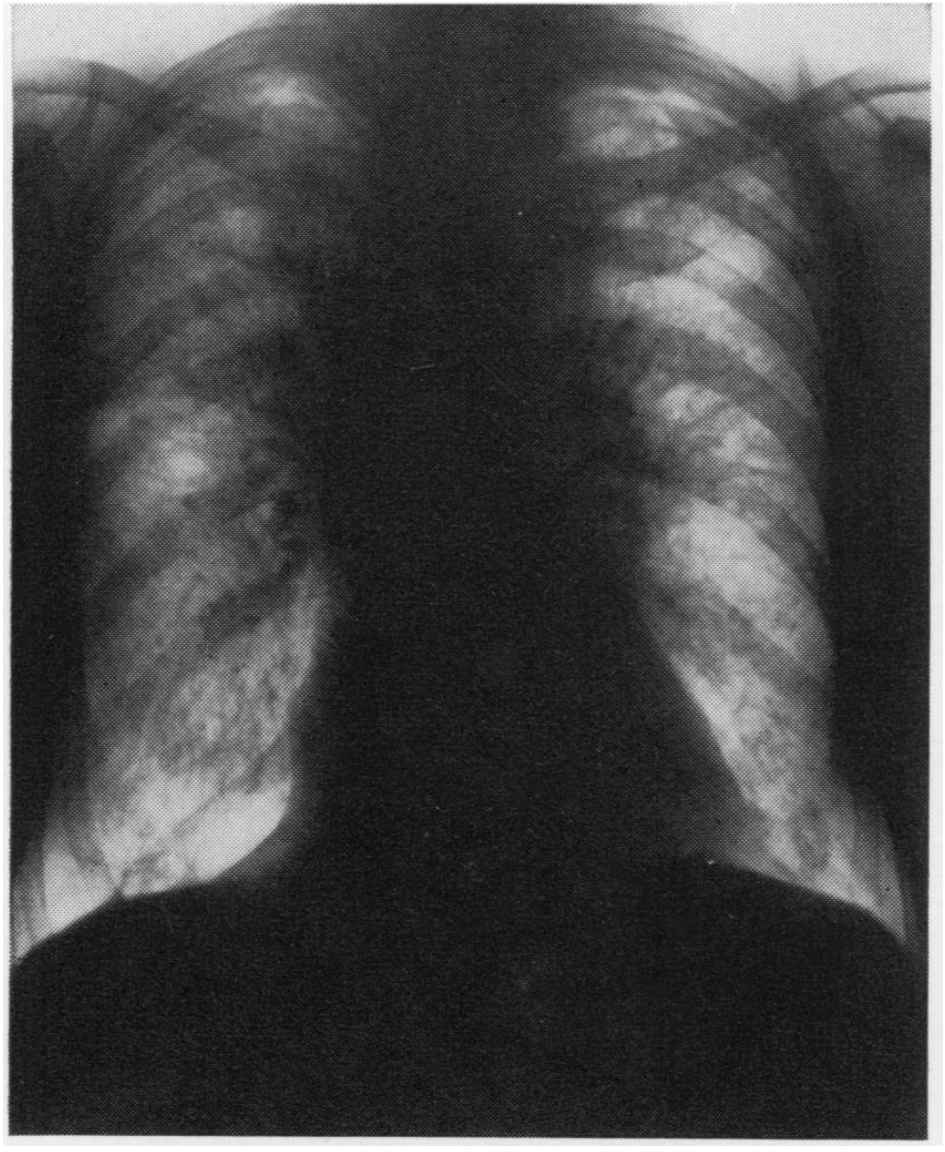


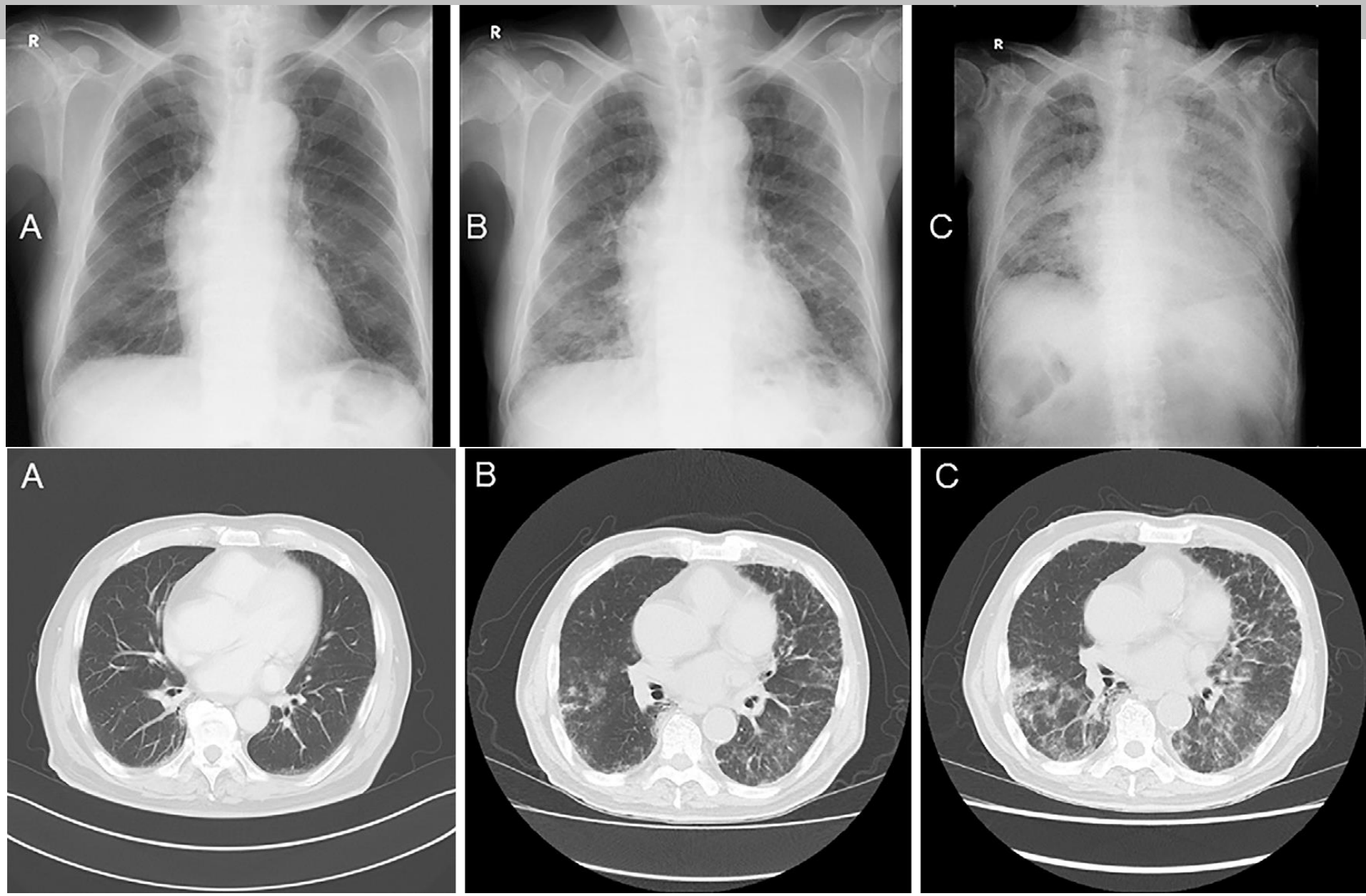
Figure 1. Algorithme diagnostique de la fibrose pulmonaire idiopathique. FPI, fibrose pulmonaire idiopathique ; PIC, pneumopathie interstitielle commune ; PID, pneumopathie interstitielle diffuse, TDM, tomodensitométrie.

1-Médicaments indiscutables –Codling 1972: melphalan





Hydroxycarbamide (**Imai, 2015**)



ORIGINAL ARTICLE

Chronic Nitrofurantoin–Induced Lung Disease

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

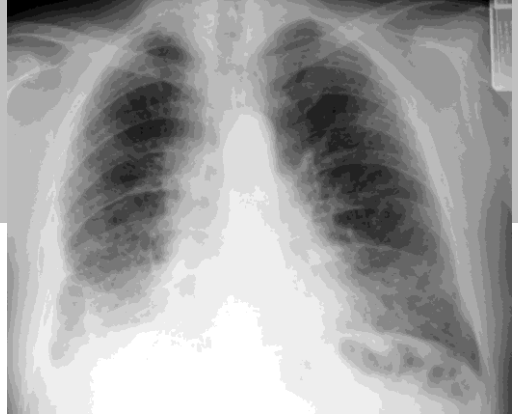
OBJECTIVE: **To reassess the clinical and radiological features of chronic nitrofurantoin–induced lung disease and eventual clinical outcome.**

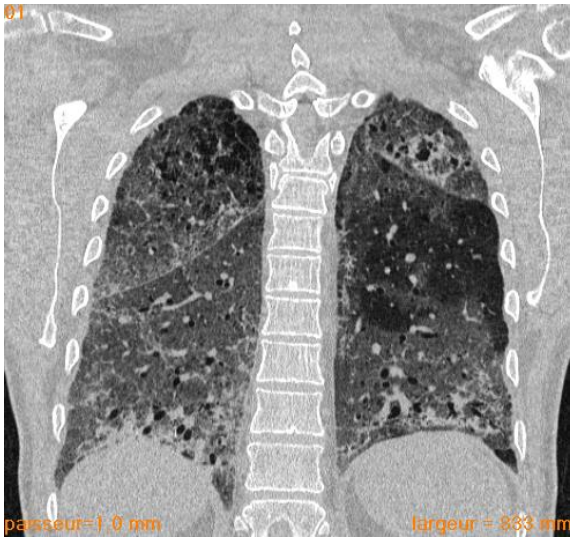
PATIENTS AND METHODS: **We retrospectively reviewed the medical records of 18 patients with chronic nitrofurantoin–induced lung disease who were seen at the Mayo Clinic in Rochester, Minn, from January 1, 1997, to December 31, 2002.**

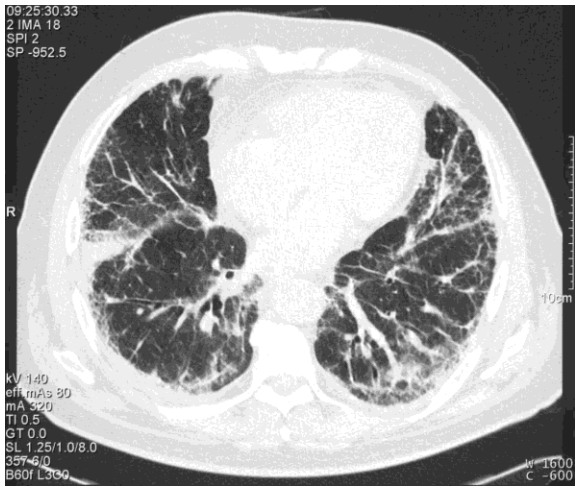
RESULTS: **The median age of the 18 patients was 72 years (range, 47-90 years) at the time of diagnosis; 17 (94%) were women. Onset of symptoms occurred after a median interval of 23 months (range, 10-144 months) following the initiation of nitrofurantoin therapy for the prevention of recurrent urinary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

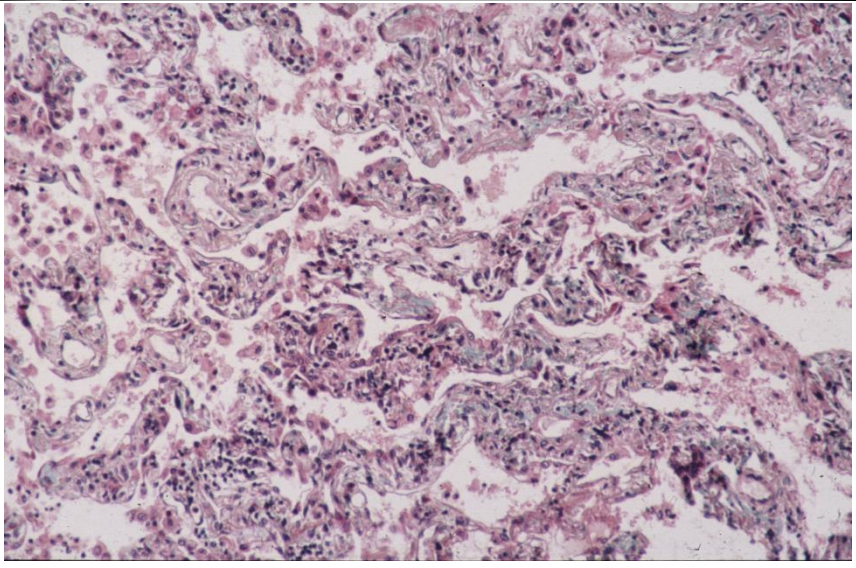
- 18 patients (17F)
- M >23 mois
- Délai diagnostique: 4 mois
- Eosinophilie périphérique: 17%
- Biopsies: PINS, BOOP, GIP
- Eviction: 18/18
- Corticoïdes: 9/18
- Amélioration: 16
- Stablilité: 2
- Séquelles 12

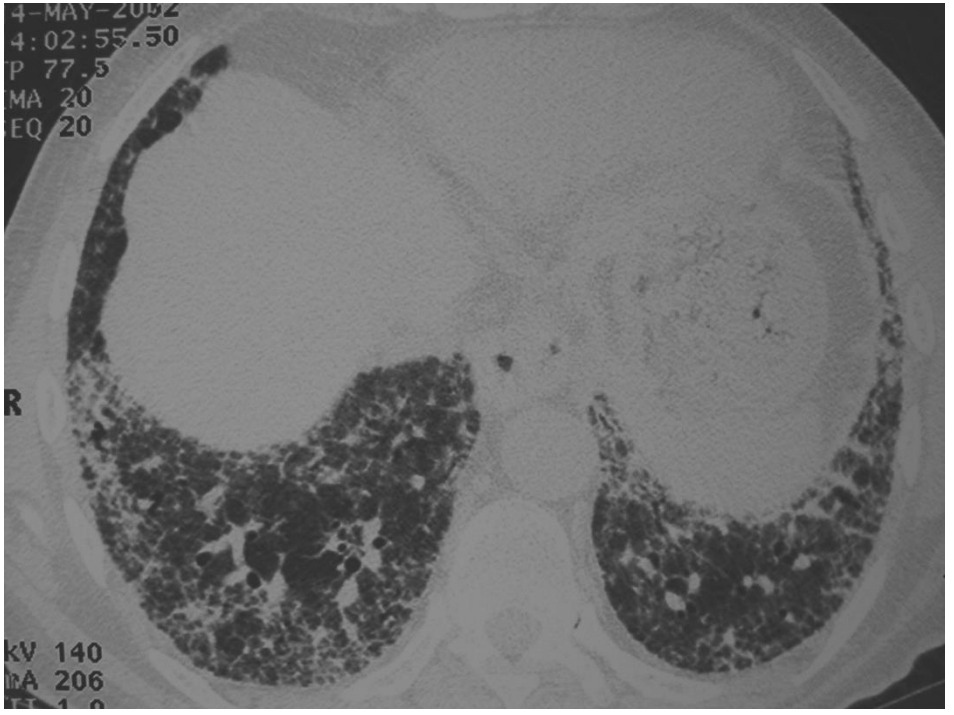






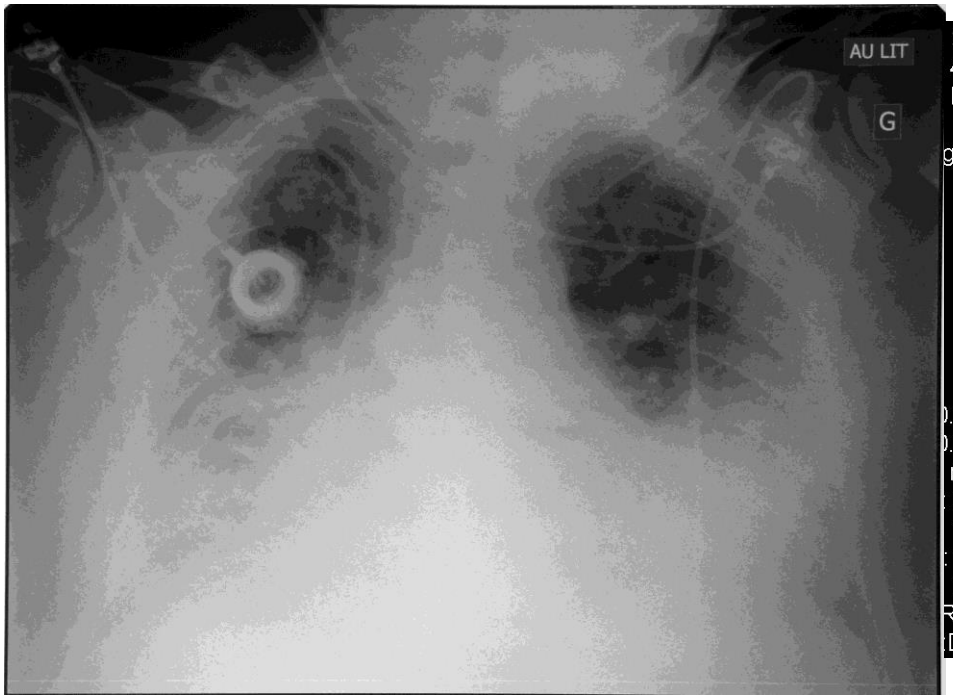
Amiodarone 10-50%





2-Fibroses accélérées

- Adalimumab
- Amiodarone
- Bleomycin
- Certolizumab
- Chemotherapy, antineoplastic
- Erlotinib
- Etanercept
- FOLFOX
- Infliximab
- Interferon gamma
- Medroxyprogesterone
- Methotrexate
- Mitomycin C
- Organophosphates
- Paclitaxel
- Paraquat
- Parathion
- Pemetrexed
- Penicillamine
- Radiation therapy, infusional (injected 131I or 90Y radioactivity)
- TNF-alpha antagonists/inhibitors


AU LIT
G

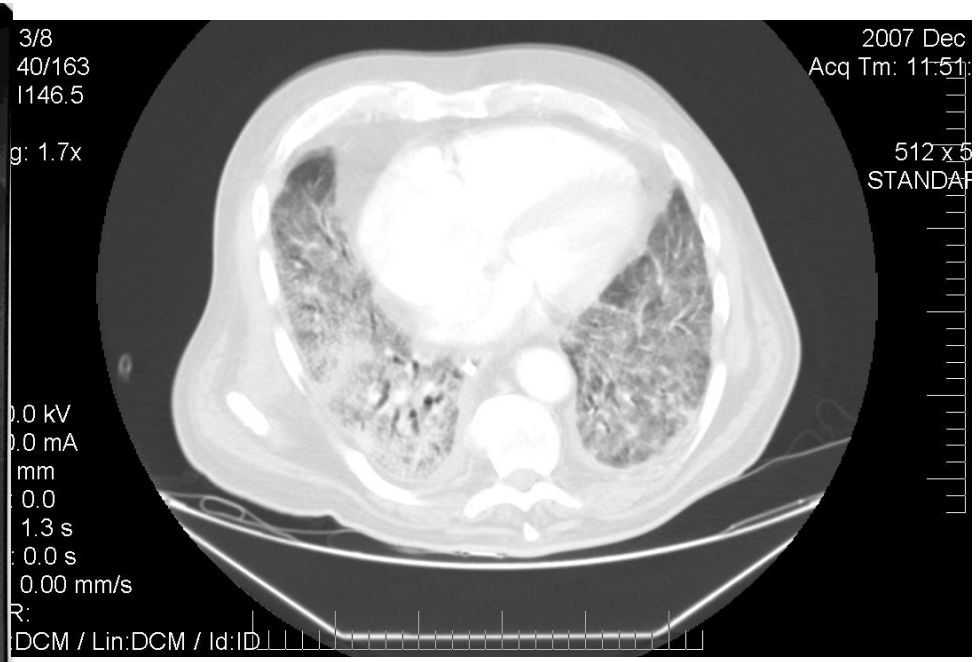
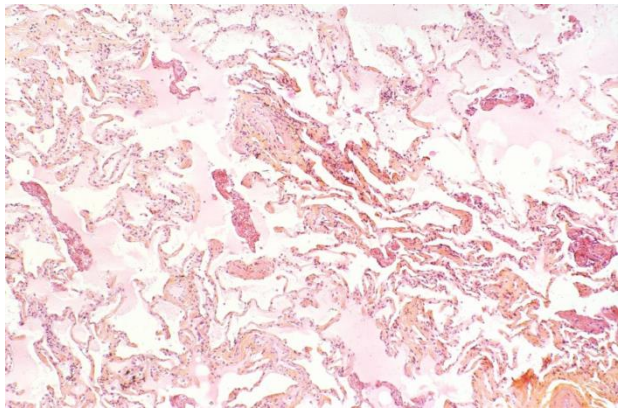

3/8
40/163
I146.5
g: 1.7x
2007 Dec
Acq Tm: 11:51
512 x 5
STANDAR
.0 kV
.0 mA
mm
0.0
1.3 s
0.0 s
0.00 mm/s
R:
DCM / Lin:DCM / Id:ID

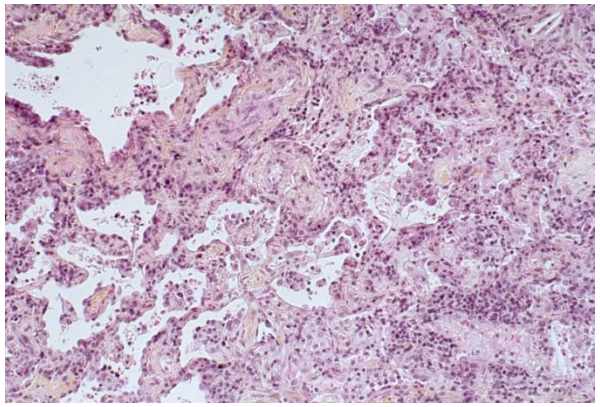
Fig. 1. A chest radiograph shows bilateral pulmonary infiltrates and extensive subcutaneous emphysema. Bilateral chest tubes are in place for pneumothraces.

Fig. 2. A computerized tomography of the chest shows pneumomediastinum and extensive subcutaneous emphysema.

3-Fibroses en histologie (PINS-f) honeycomb rare

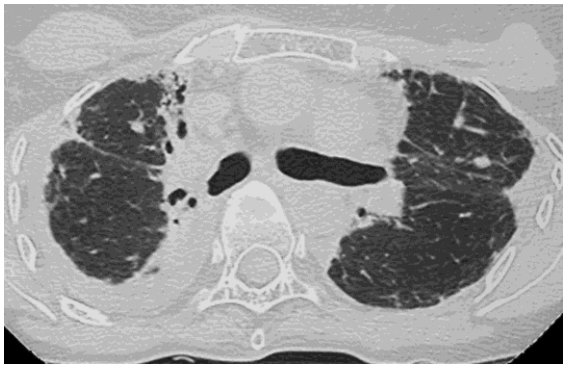
- Amiodarone
- Bleomycine
- Busulfan
- Carmustine (BCNU)
- Chlorozotocine (DCNU)
- Cocaine
- Cyclophosphamide
- Docetaxel
- Ifosfamide
- Melphalan
- Nitrofurantoine
- Nitrosourées
- Paclitaxel
- Paraffine
- Paraquat
- PTU
- Irradiation

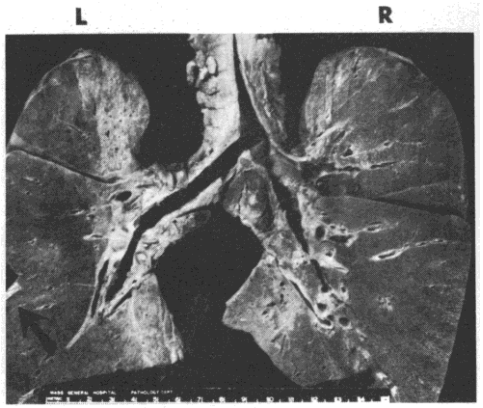


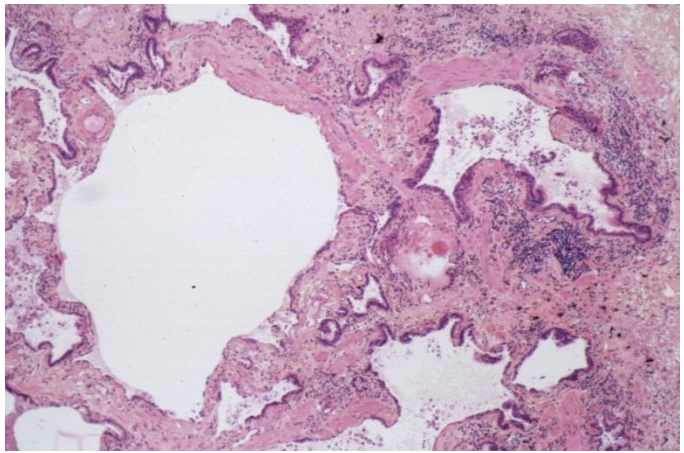


4-Histologie ‘UIP’/PIC rayons de miel

- Amiodarone
- Azathioprine
- Flecainide
- Gefitinib
- Ifosfamide
- Melphalan
- Nitrofurantoïne
- Radiations
- Rituximab







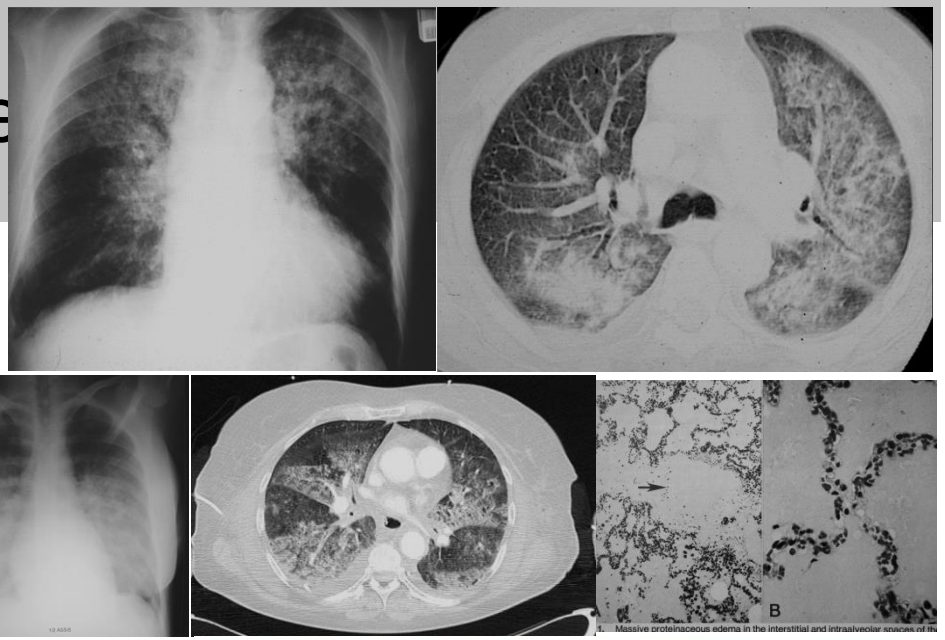
5-Exacerbation aiguë de FID/PIC

- Définition
  - Aggravation symptomatique
  - <30 j
  - Hypoxémie
  - Modification radiographique
- Ryerson et al. 2015
  ‘*The risk of drug-induced exacerbation appears to be higher in patients with underlying UIP compared with patients with other pre-existing patterns*’

Médicaments

- Amiodarone
- Nitrofurantoïne
- Chimiothérapies anticancéreuses
- Anti-PD1/CTLA4 (mélanomes, autres tumeurs)
- Anti-TNF alpha
- Statines

OAP & Œdème pulmonaire



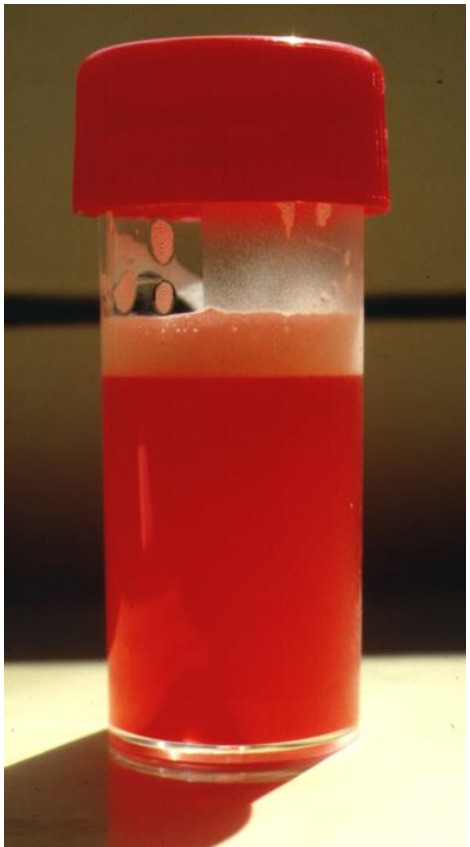
- N=190
  - Produits de contraste
  - Adrénaline
  - Vasoconstricteurs
  - Chimiothérapies
  - Aspirine
    - Saturation mb >300 mg/L (5-6 g)
    - Acidose métabolique
  - Sang et dérivés
    - TRALI immun/nonimmun
  - IVIG, ATG
  - Héroïne

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

- NONCARDIOGENIQUE vs. CARDIOGENIQUE

Hémorragie alvéolaire DAH/HAD

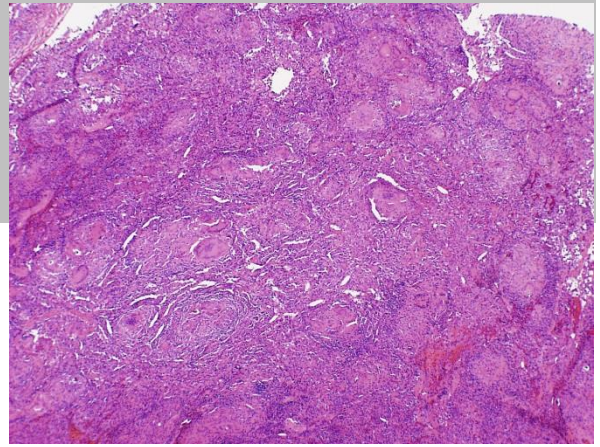
- N=125
  - AVK
  - Superwarfarines
  - *I*-GP IIB-IIIA plaquettaires
  - NACO
  - Fibrinolytiques
  - I-mTOR
  - Amiodarone
  - ATRA
- Bland vs. autoanticorps



Formes rares

- DIP
- LIP
- GIP
- RB-ILD
- PAP
- ‘Brownish’ DIP
- Hystiocytoses

Particularités médicamenteuses



- Etanercept
  - Images réticulonodulaires
  - Ana-path
    - PnI aiguë granulomateuse, non nécrosante
    - PnP fibrineuse
    - Fibrose interstitielle
    - Colorations spéciales et cultures -
      - Réaction médicamenteuse?
      - Microorganisme?
      - *Forme fruste* de nodules rheumatoïdes?

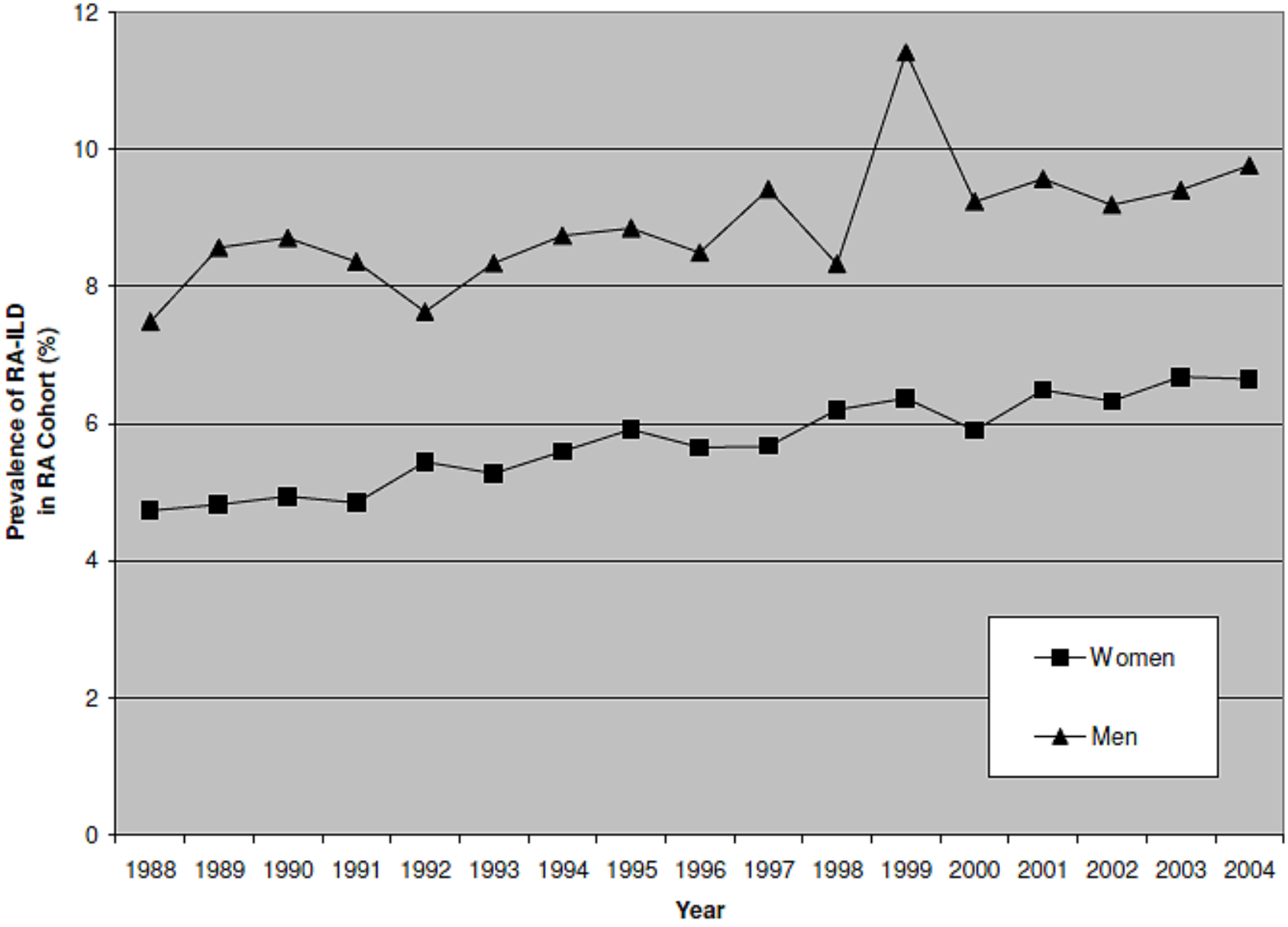
Peno-Green. 2002; Phillips 2005; Yousem 2005

Anti TNF-alpha et ‘ILD’

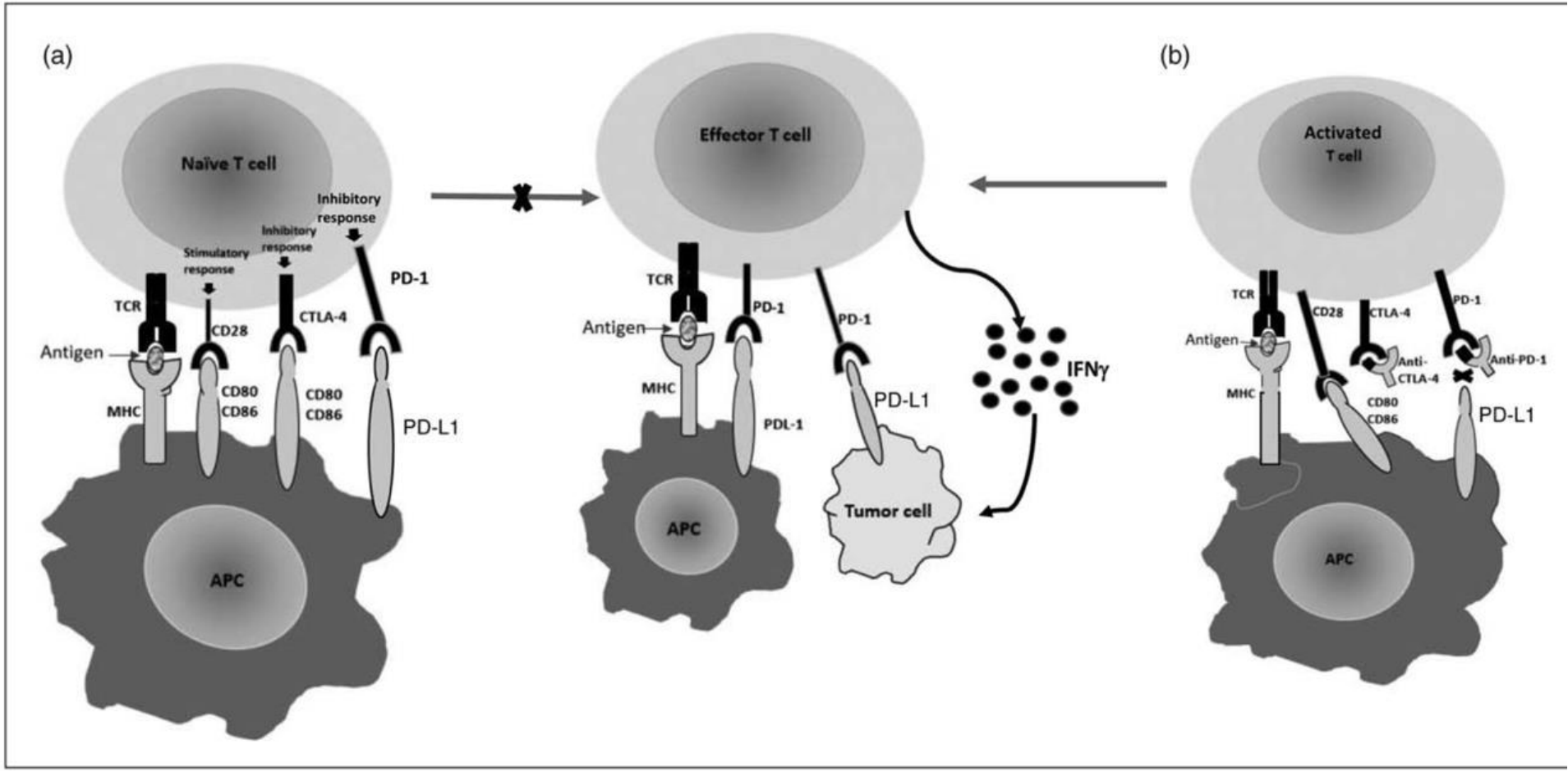
- Infliximab
  - PIE: 1 (HACA)
  - HA: 1
  - PnI aiguë évoquant PnI du MTX > début du ttt: 3
  - PnI-DAD acceleré : 20 (18 PR)
    - 1-to-3 perfusions
    - Médicaments concomitants: 10
    - Décès: 10

Anti-TNF: Dixon *et al*. 2010

- RR de mortalité globale
  - DMARDs : 1
  - Anti-TNF: 0,81 (0.38-1.73)
- Mortalité par ‘ILD’
  - Anti-TNF 15/70 (21%)
  - DMARDs 1/14 (7%)
- Conclusion
  - Mortalité PR + ‘ILD’ non différente sous anti-TNF therapy *vs*. DMARDs conventionnels
  - Proportion de décès attribuables à la PnI plus élevée sous anti-TNF
  - Biais de reporting possible


Prevalence of RA-ILD in RA Cohort (%)
12
10
8
6
4
2
0
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
Year
Women
Men

Immunotherapy – Immune checkpoint inhibitors (ICPI)

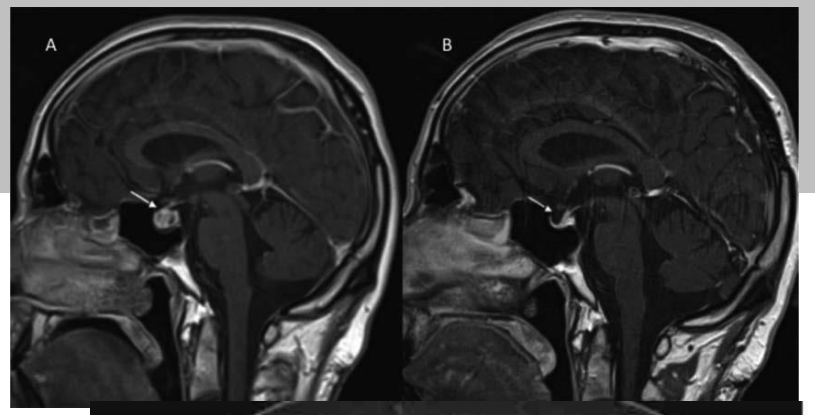


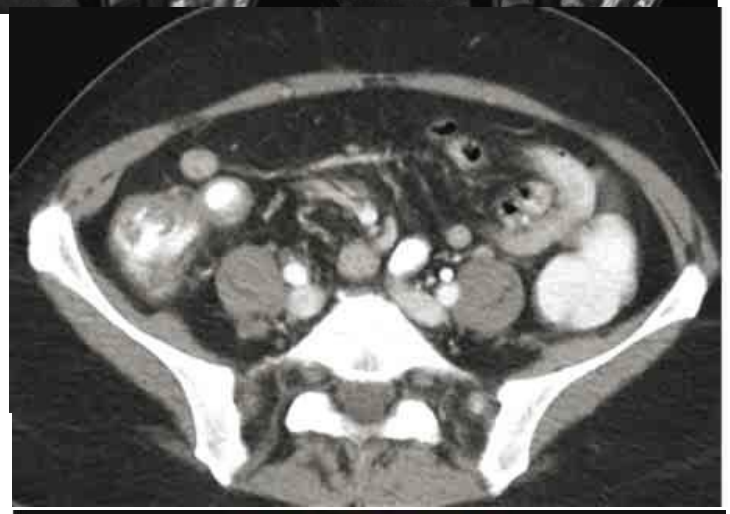
ICPIs

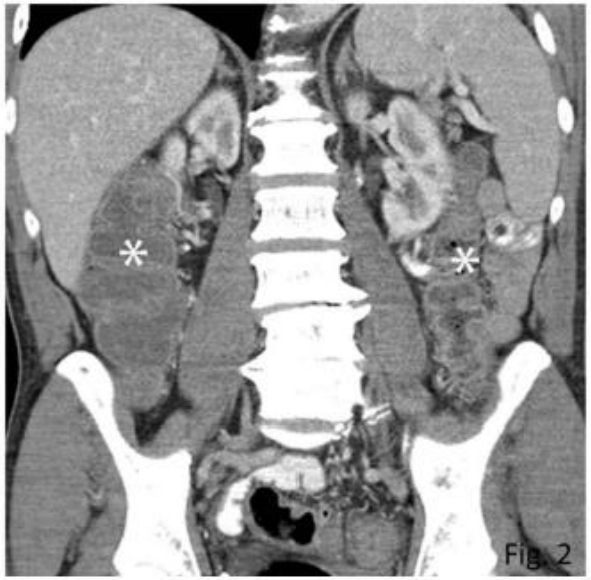
- CTLA4
  - Ipilimumab (Yervoy®)
  - Tremelimumab
- PD1
  - Nivolumab (Opdivo®) 2014
  - Pembrolizumab (Keytruda®)
  - Both IgG4 kappa 146-149 kDa. Low immunogenicity
- PDL1
  - Atezolizumab (Tecentriq®) 2016
  - Durvalumab MEDI-4736
  - Avelumab
- Other payhways
  - Inhibitory immune signals: LAG-3,TIM-3,VISTA,BTLA
  - Stimulatory immune signals ICOS,OX40,41BB

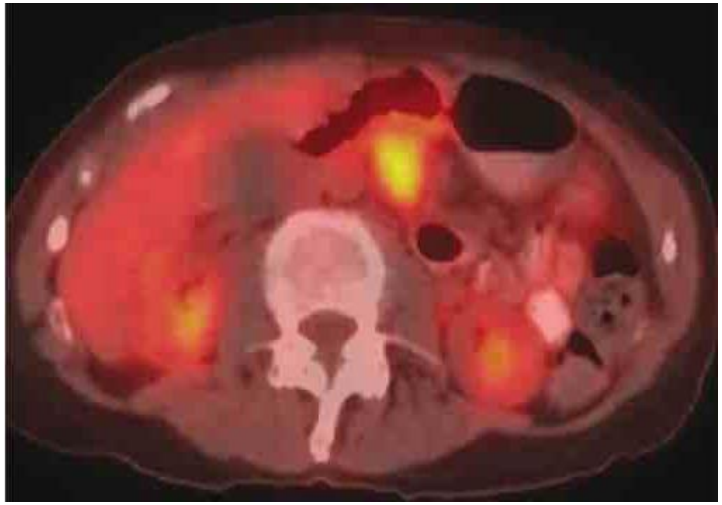
Adverse effects (<1% fatal)

- Low *v*. high grade ¾ - ¼
- Skin rash: 44%
- GI tract: 35%
- Hypophysitis: 13%
- Endocrine: 6%
- Hepatic: 5%
- *Neurologic*
- *Pulmonary*
- *Renal*
- *Cardiac*
- *Pericarditis*
- *Uveitis*
- *Alopecia*
- *Vitiligo*









Koelzer

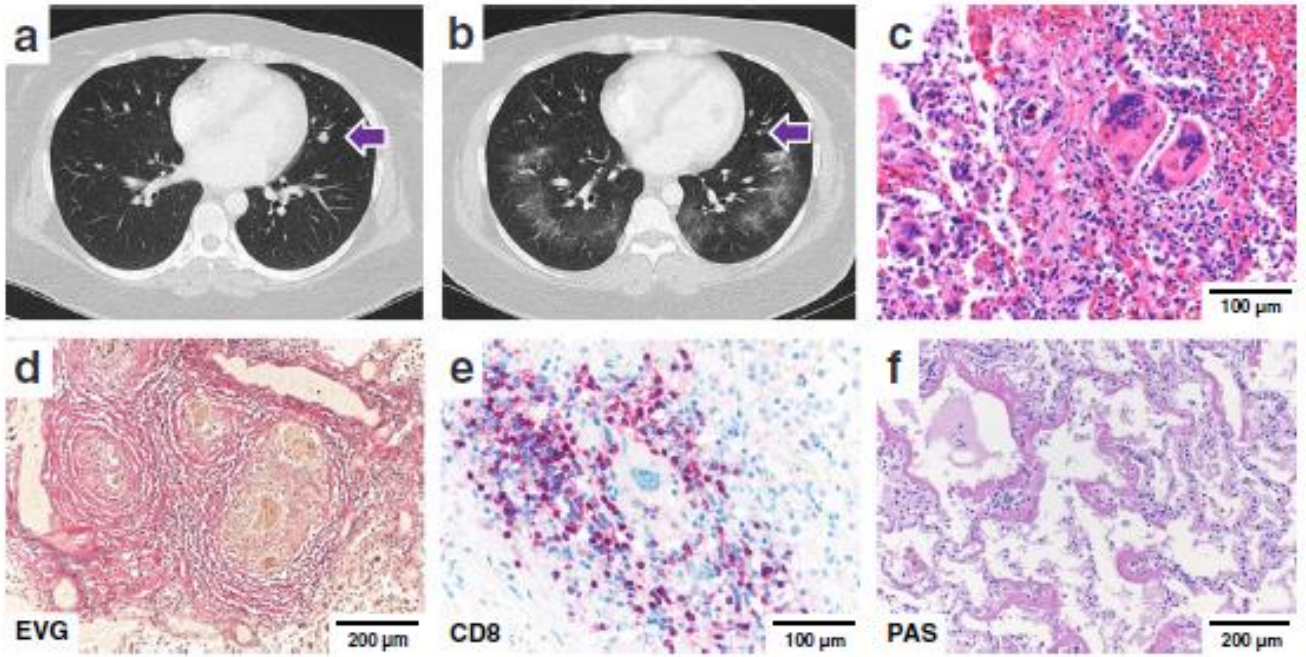


Fig. 3 Lung damage patterns. **a** CT Thorax: Pulmonary metastasis before therapy with Ipilimumab (02/2015) **b** CT Thorax: pulmonary metastasis regression, ground glass opacities after Ipilimumab (04/2015) **c** sarcoid-like reaction **d** elastica stain showing epithelioid granulomas surrounded by fibrotic rings **e** CD8-positive T-cell infiltrates surrounding giant cell granulomas as detected by immunohistochemistry **f** diffuse alveolar damage; scale bars as indicated

Immunotherapy – Immune checkpoint inhibitors (ICPI)

- Distinctive/Unique spectrum of AEs
- Pneumonitis relatively common, potentially fatal
- Incidence PD1>PDL1>CTLA4
- Incidence higher in lung and renal cancers/melanoma
- Combo -> higher incidences
- Risk factors: lung cancer, ?tobacco, ?preexisting ILD
- Infiltration of highly activated CD4/CD8 Tcells
- Early diagnosis imperative
- May be dismissed as disease progression
- Bilateral GGO or consolidation
- Compatible interval
- Corticosteroid therapy (in severe or prolonged pneumonitis cases) essential
- Rechallenge can be contemplated

Pathophysiology

- Rodent models

Immunity, Vol. 3, 541–547, November, 1995, Copyright © 1995 by Cell Press

Loss of CTLA-4 Leads to Massive Lymphoproliferation and Fatal Multiorgan Tissue Destruction, Revealing a Critical Negative Regulatory Role of CTLA-4

- Spontaneous defects in ICP signaling in man
- Similarities with ICPI

Pneumonitis: Incidence in NSCLC

- Garon et al. 2015. Pembrolizumab
  - Any grade 3.6%
  - Grade III-V: 1,8
- Reck *et al.*, 2016. Keynote-024
  - Any grade 5.8%
  - Grade III-V: 2.6%
  - *vs*. 0.7% platinum-based chemo
- Combined ICPI
  - NSCLC ~5% (Spain *et al*.)
  - (*v*. melanoma: 2%)

Chest 2017, *in press*

Incidence of pneumonitis with use of PD-1 and PD-L1 inhibitors in non-small cell lung cancer: A Systematic Review and Meta-analysis of trials

Monica Khunger MD[1], Sagar Rakshit MD[1], Vinay Pasupuleti MD, PhD[2], Adrian V Hernandez MD, MSc, PhD[3], Peter Mazzone, MD, MPH, FCCP[4], James Stevenson, MD[5], Nathan A Pennell, MD PhD[5] and Vamsidhar Velcheti MD, FACP[5]

- Terms: pneumonitis (intrestitial lung disease, and pneumonia excluded)

- Mean age 64 years
- Male 64%
- Number of patients across trials 35 - 807
- Incidence of pneumonitis:
  - All grades
    - PD-1: 3.6% (no difference nivolumab *vs*. pembrolizumab)
    - PDL-1: 1.3%
  - Grade ≥3
    - PD-1: 1.1%
    - PDL-1: 0.4%
- Treatment naïve v. previously treated: 4.3 vs. 2.8%

Timing

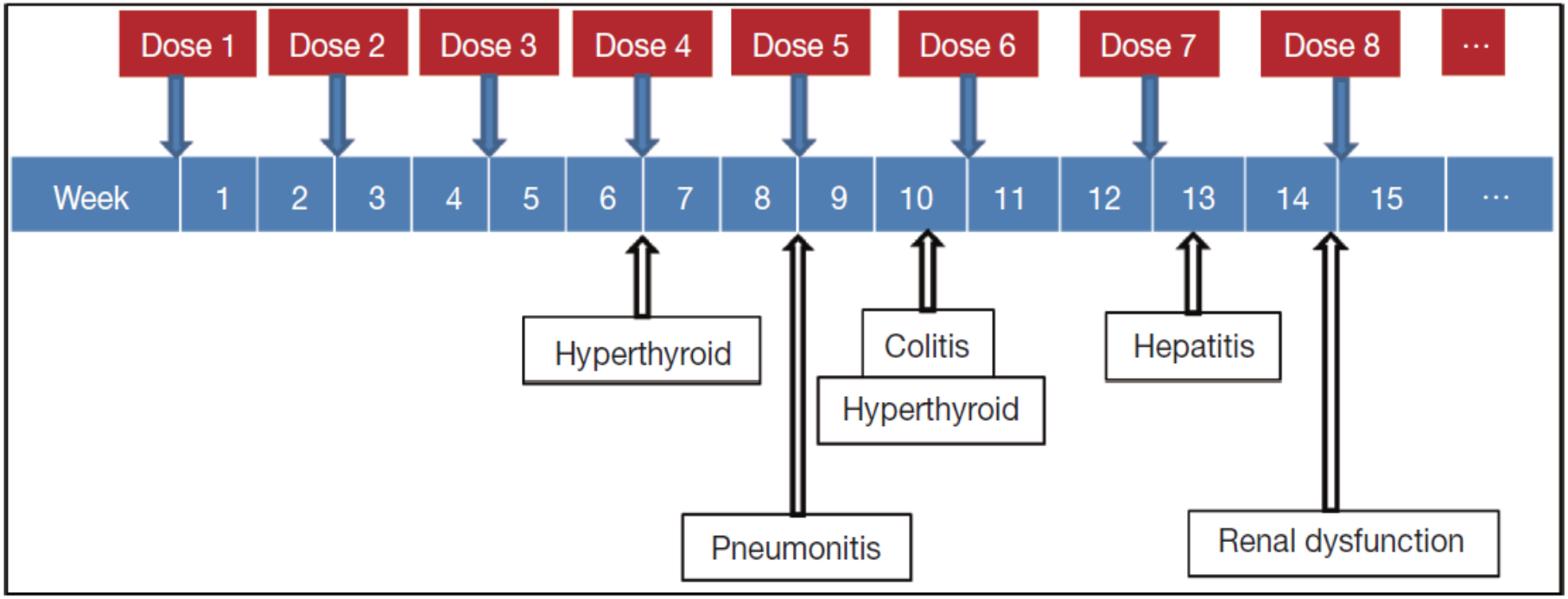


Figure 2 Median time for appearance of immune-related adverse events (irAEs) with nivolumab based on a phase III study (9).

Clinical presentation

- Dry cough
- Dyspnea (cyanosis)
- Fever-chills unusual
- Differential
  - Infectious pneumonia (*Chlamydia, Mycoplasma*)
  - Progression, tumoral inflammation
  - Exacerbation of u/l IPF
  - Congestive heart failure & pulmonary edema
  - VTE
  - Reaction to concomitant meds. / radiation therapy

Imaging

- GGO 10/27 [37%])
- Mosaic (6/27 [22%])
- Areas of consolidation (consistent with BOOP) (5/27 [19%])
- Interstitial (2/27 [7%])
- Unclassifiable (4/27 [15%])

- Extent (will guide CS therapy)
  - Mild (15/27 [56%])
  - Moderate (6/27 [22%])
  - Diffuse (6/27 [22%])

Imaging

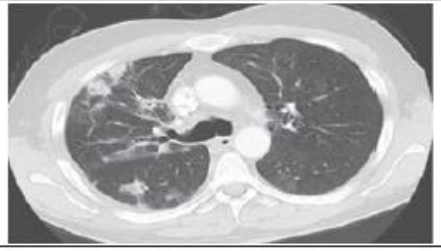
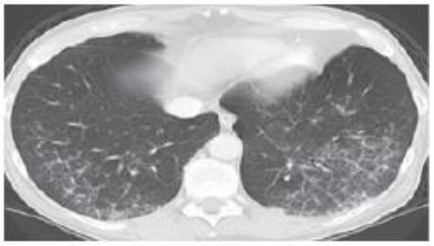
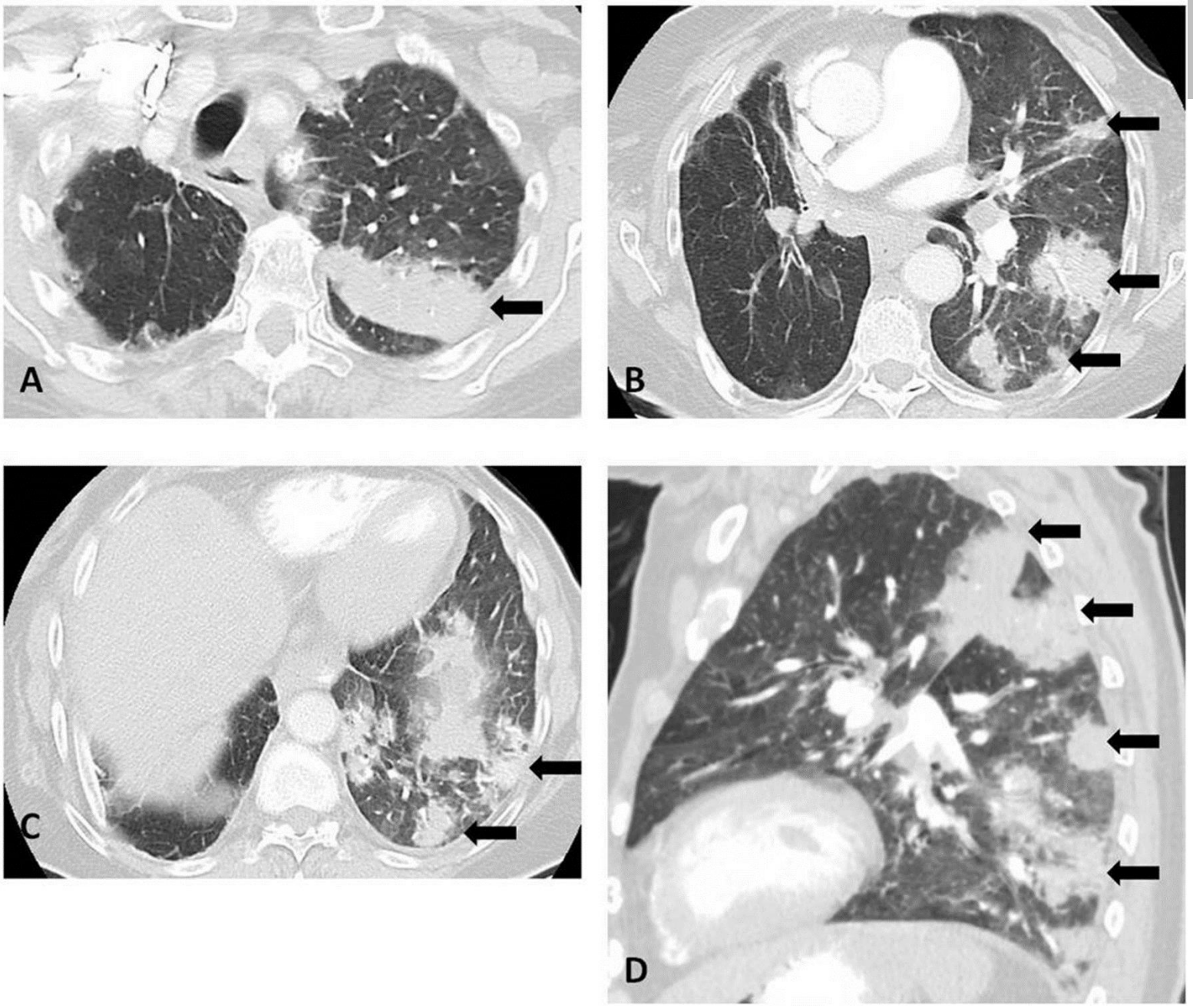
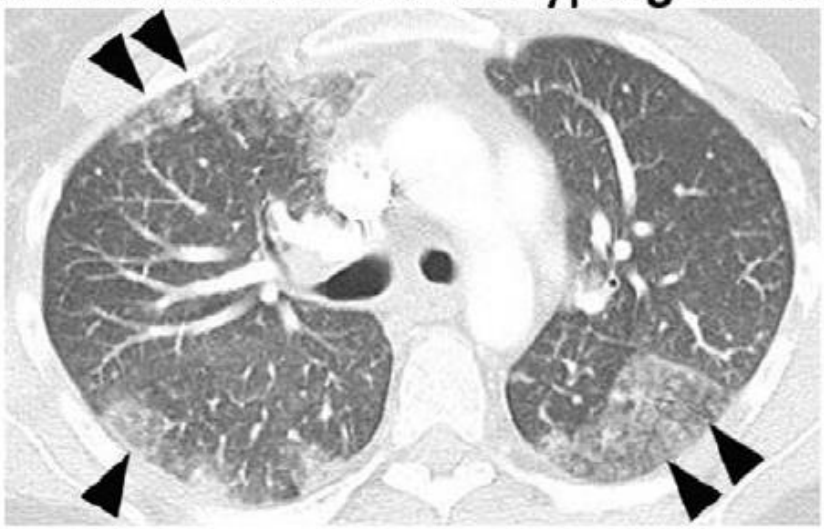
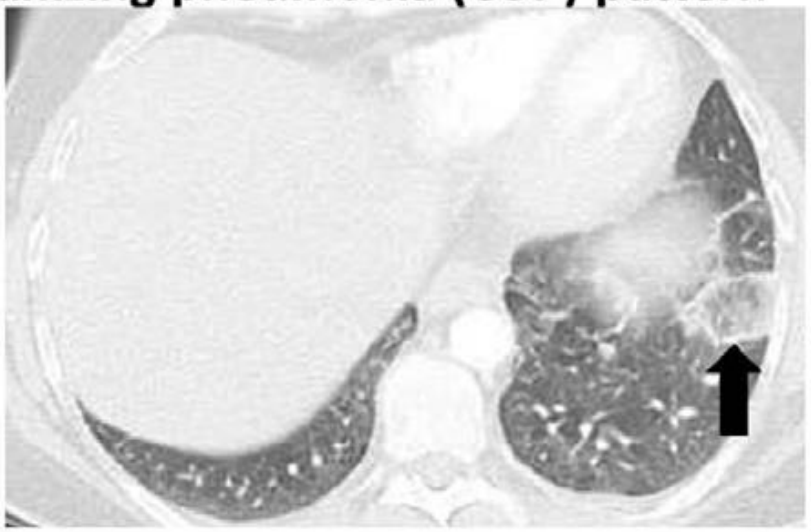
Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased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

Fig. 2.

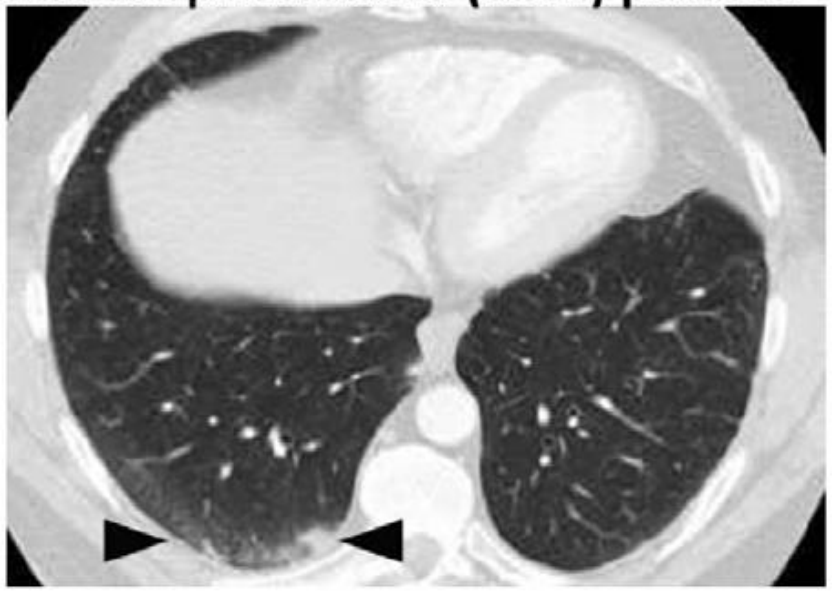


A, B. Pneumonitis with a cryptogenic organizing pneumonia (COP) pattern

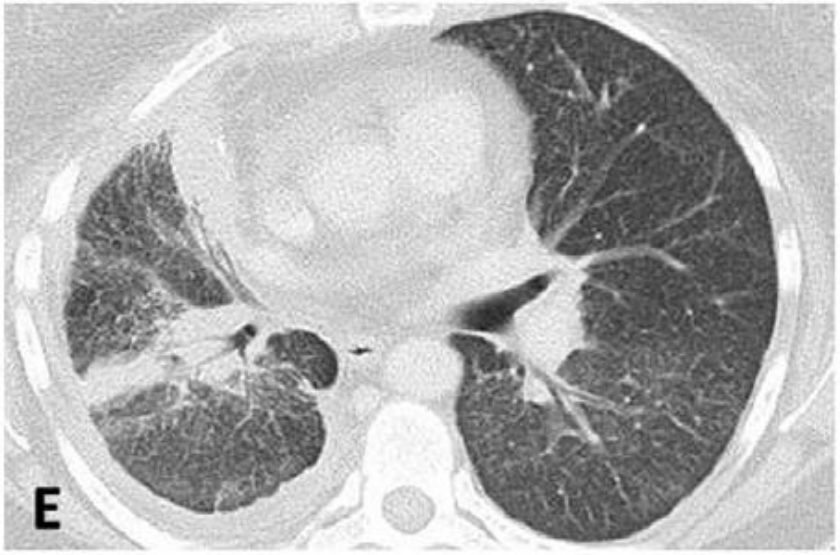


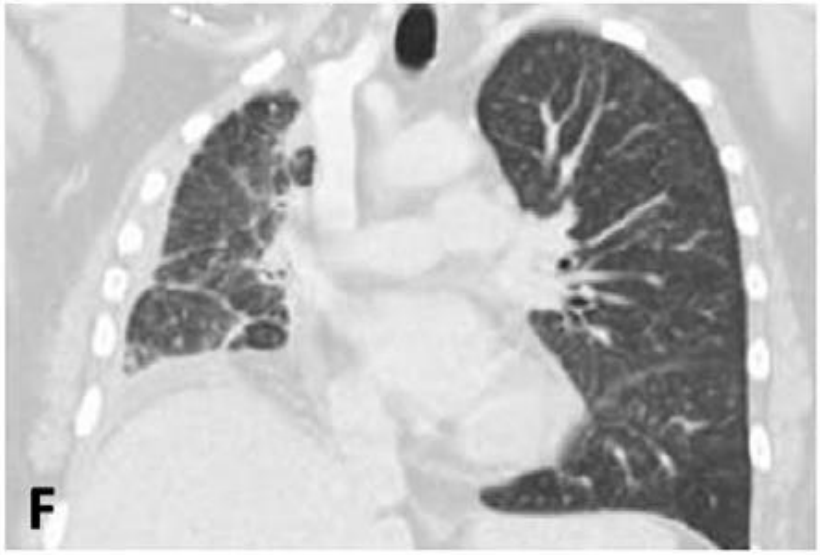


C, D. Pneumonitis with a non-specific interstitial pneumonia (NSIP) pattern

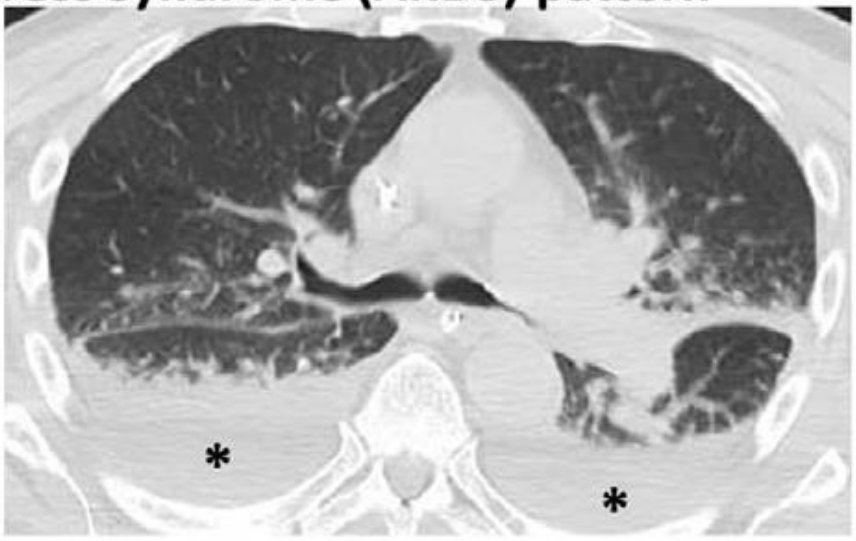


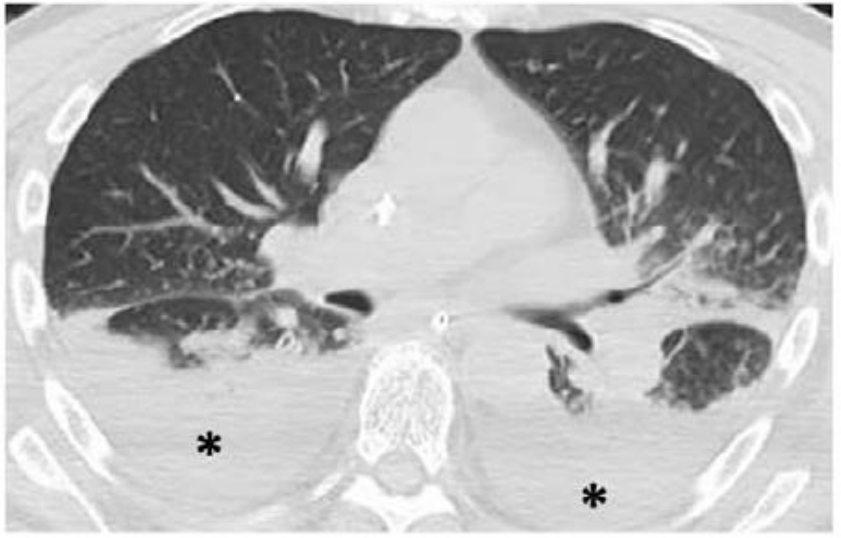
E, F. Pneumonitis with a hypersensitivity pneumonitis (HP) pattern

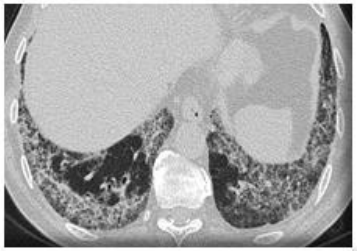


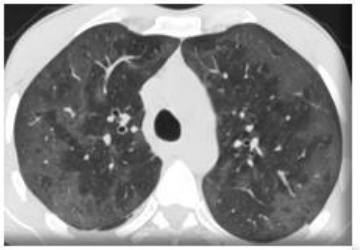


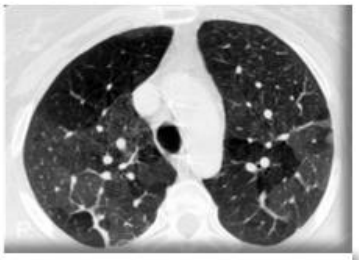
G, H. Pneumonitis with an acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern

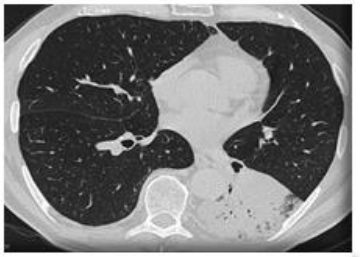


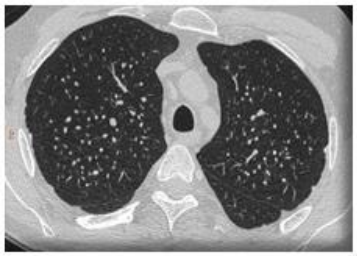


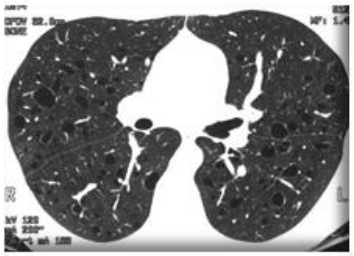


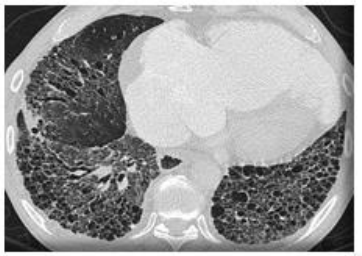




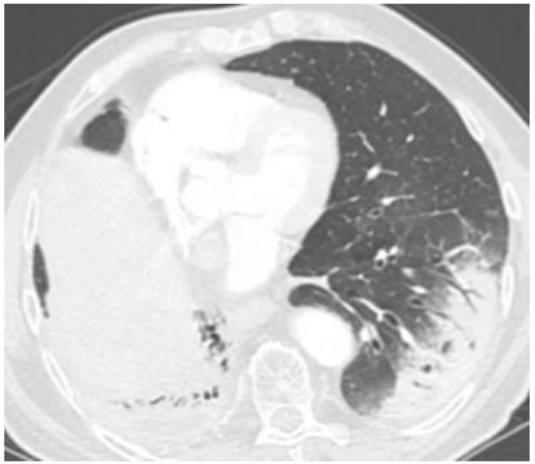


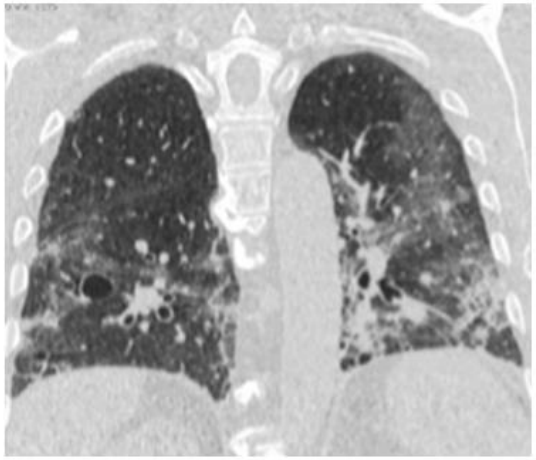


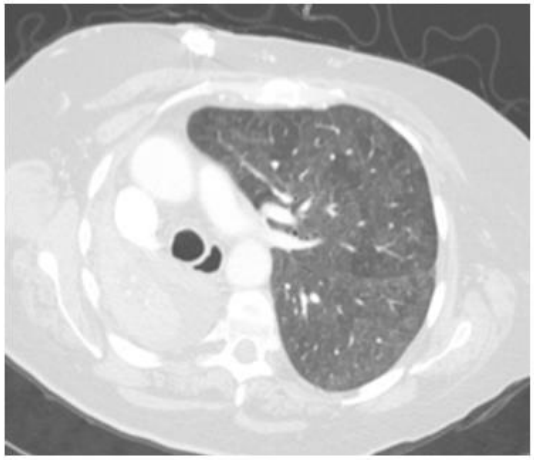


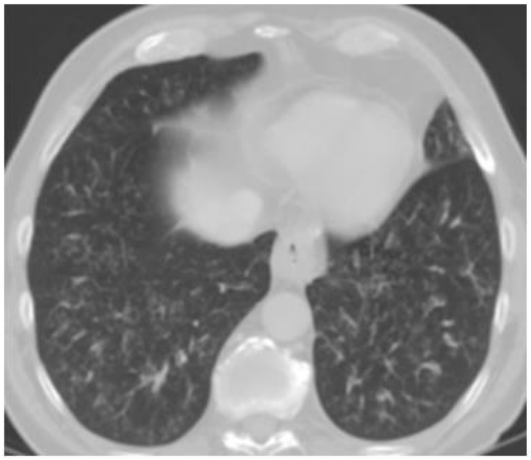


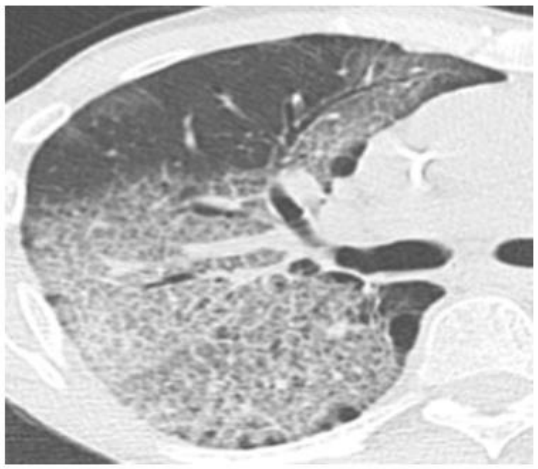
- Courtesy: J Mazieres, Toulouse, France (due to appear in Eur Respir J 2017)

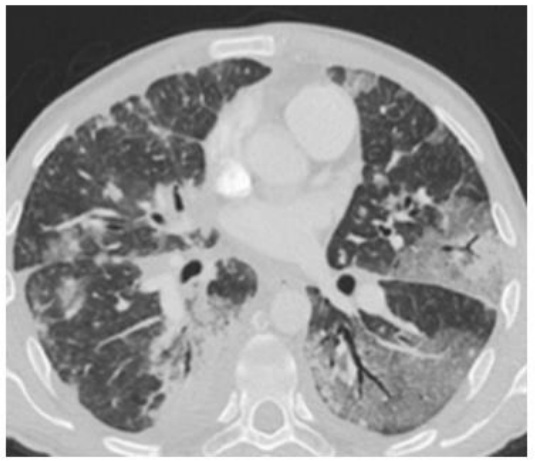


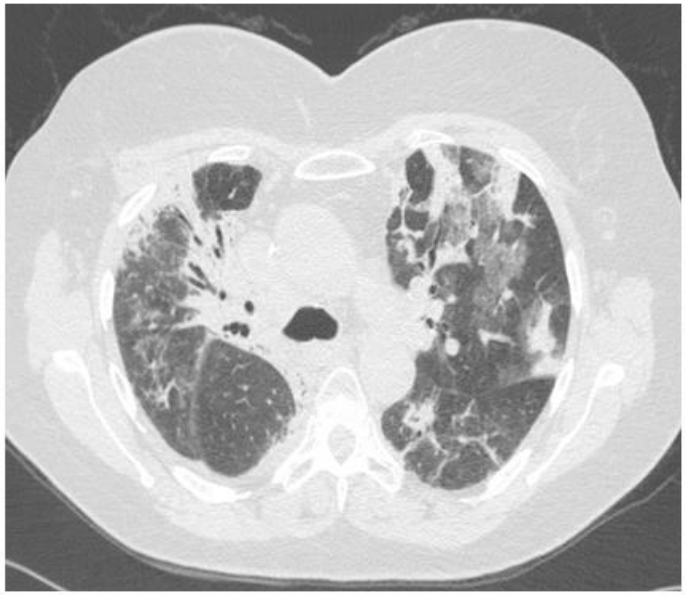
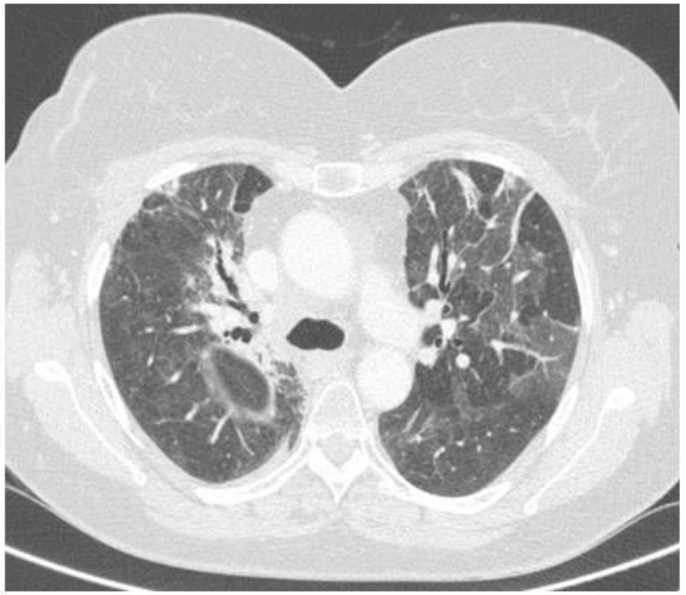
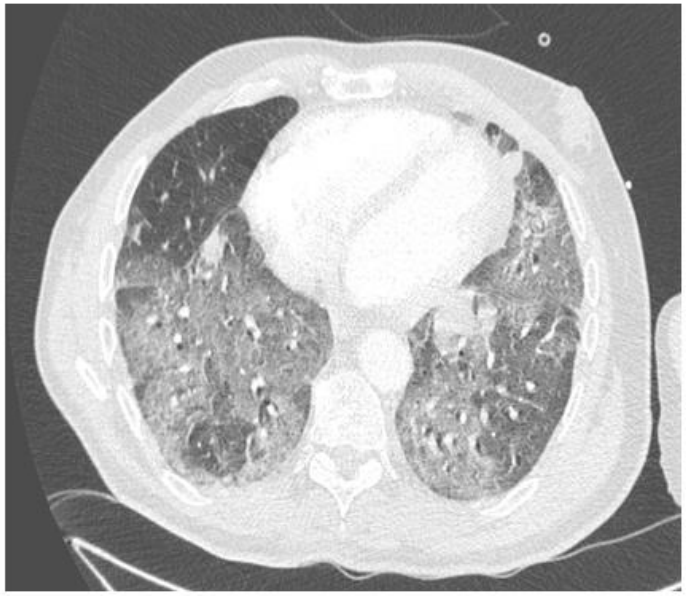
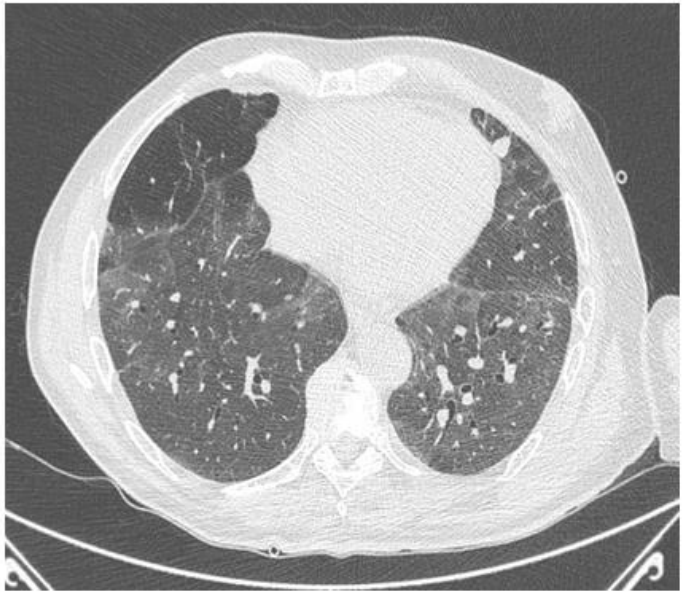


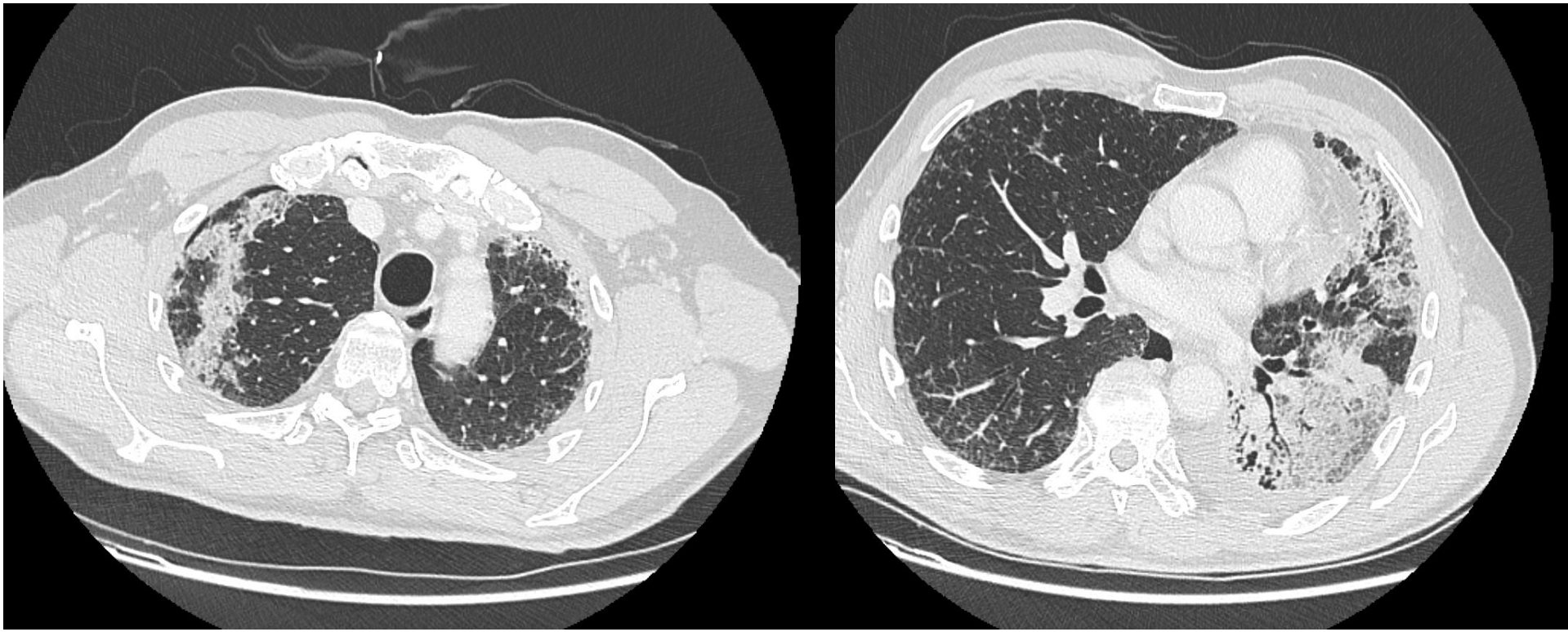




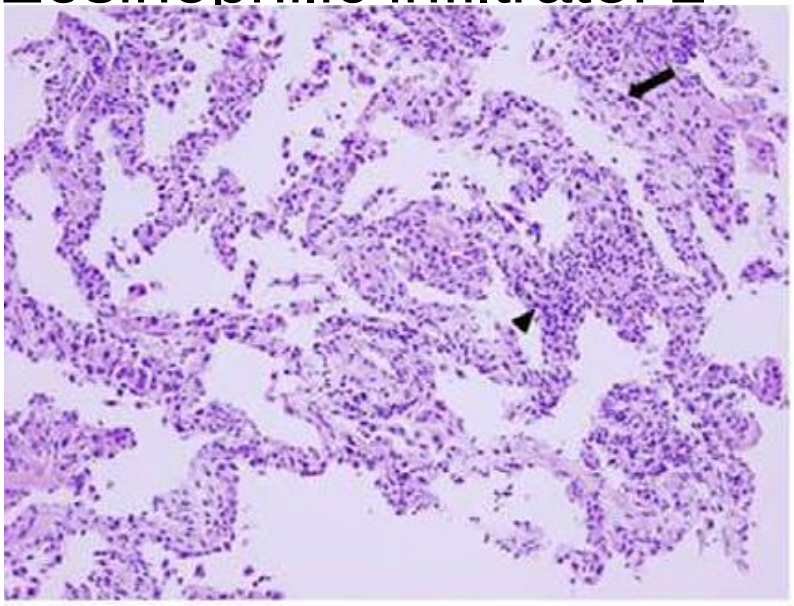


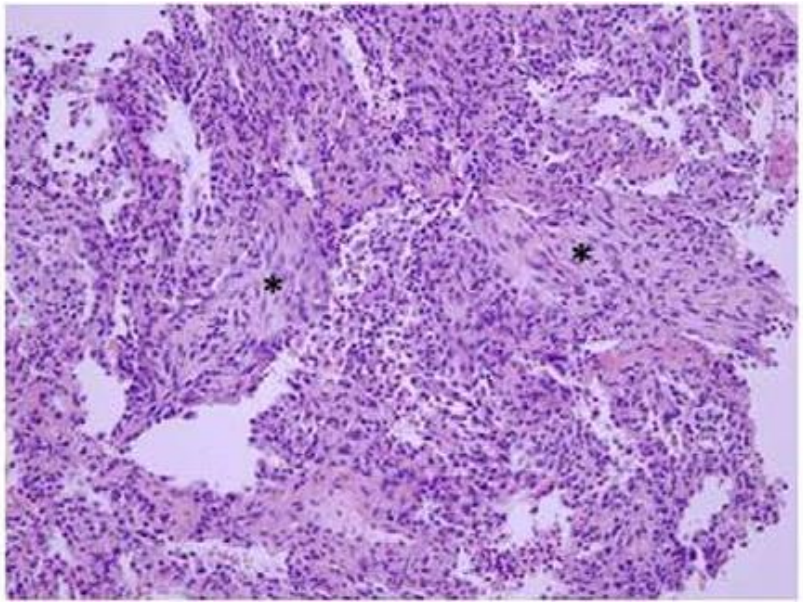




- Pathology 11/27 MSKCC underwent lung biopsy
  - Cellular IP: 4
  - BOOP: 3
  - DAD: 1
  - Poorly formed granulomas: 3
  - Eosinophilic infiltrate: 2





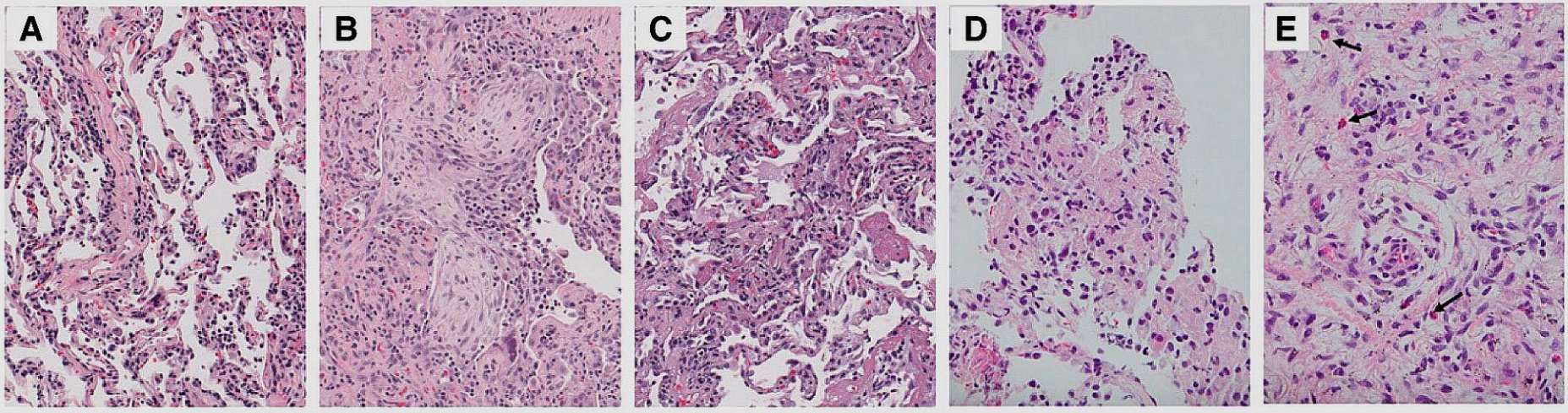
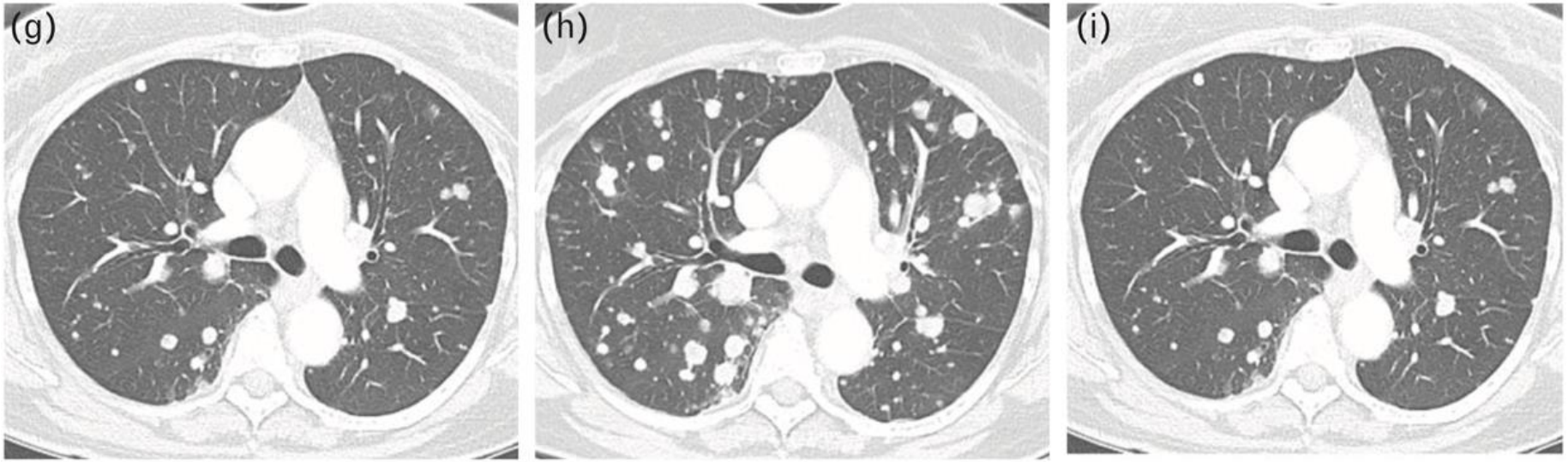


Fig A2. Histologic patterns of pneumonitis associated with anti–programmed death-1/programmed death ligand 1 therapy on lung biopsy (hematoxylin and eosin [HE] stain magnification, ×200) included (A) cellular interstitial pneumonitis (mild case shown), (B) organizing pneumonia, and (C) diffuse alveolar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

- Pseudoprogression



- Tanizaki *et al*.

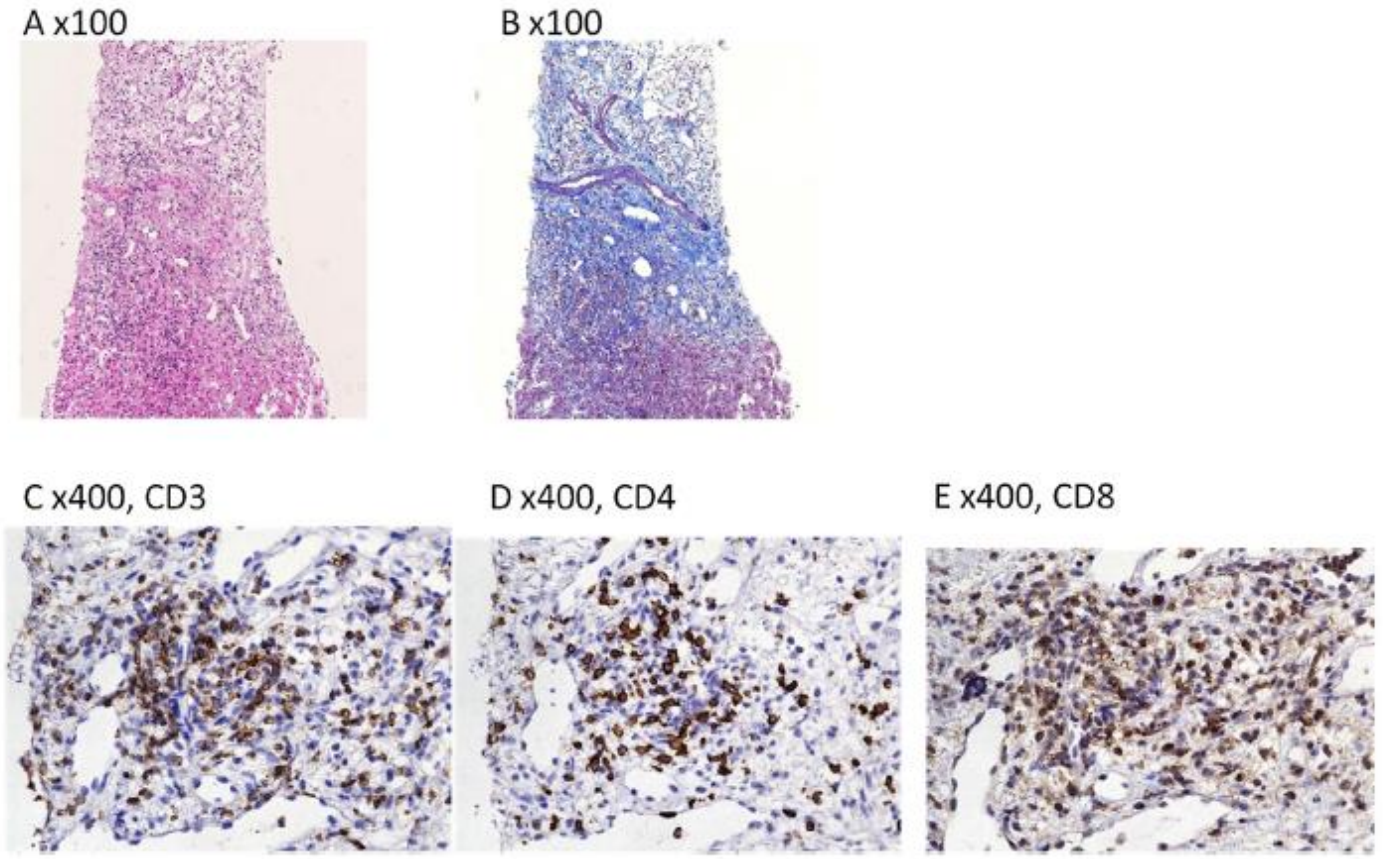


Fig. 2. Histology including immunostaining for a biopsy specimen of the liver metastatic lesion for case 1 at 18 weeks after initiation of nivolumab treatment. (A) Hematoxylin-eosin staining. (B) Masson trichrome staining. (C–E) Immunohistochemical staining of CD3 (C), CD4 (D), and CD8 (E).

ICPI IRAE: Management

Table 4. Pneumonitis Grading as per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 [43]

Grade	**Pneumonitis: a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma**
1	Asymptomatic Clinical or diagnostic observations only Intervention not indicated
2	Symptomatic Limiting instrumental activities of daily living Medical intervention indicated
3	Severe symptoms Limiting self-care activities of daily living Oxygen indicated
4	Life-threatening respiratory compromise; Urgent intervention indicated (e.g. tracheotomy or intubation)
5	Death

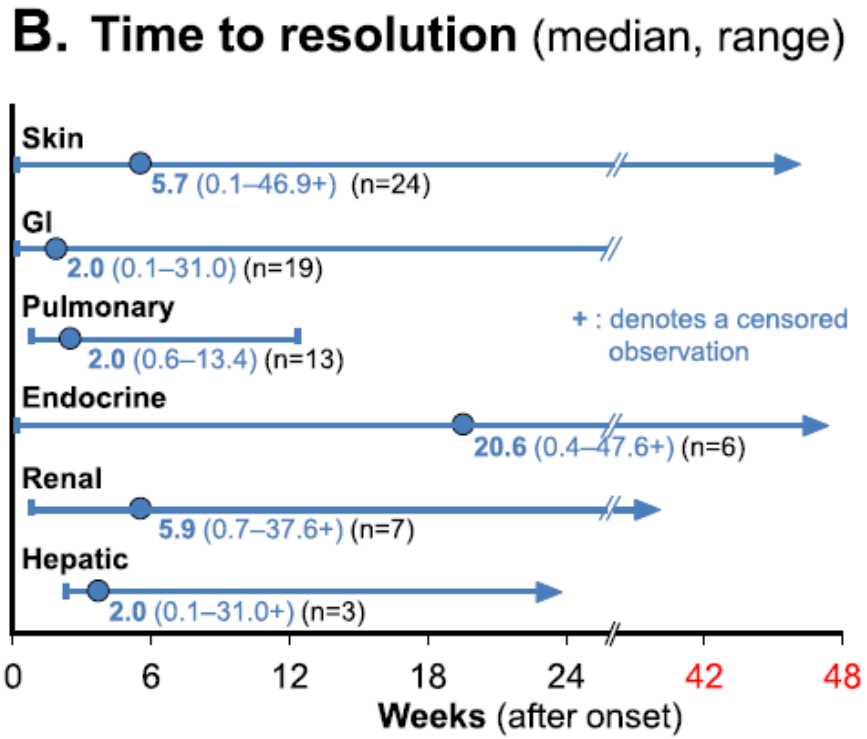
Guidelines

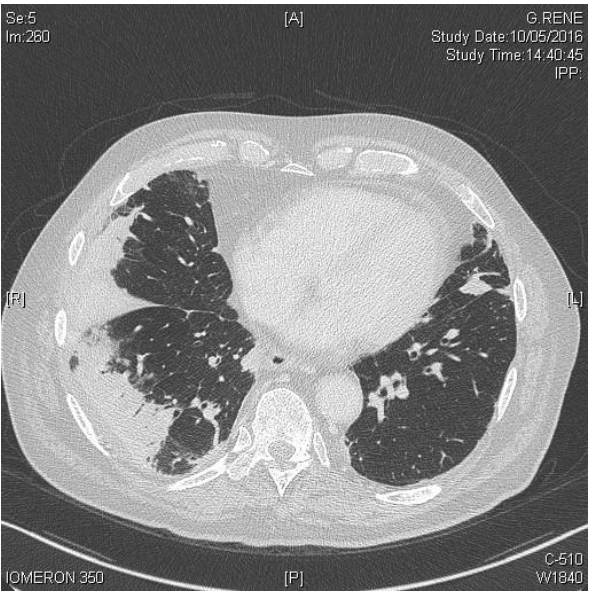
- Grade 1 (subclinical)
  - Supportive
  - Increased monitoring of symptoms
  - Exclude an infection
  - Patient education & follow-up thrice weekly
- Grade 2
  - As per grade 1 and
  - Withhold immunotherapy until toxicity has resolved ≤1
  - Consider oral steroids if persistent symptoms >5 days
  - Taper over 1 mo
  - Immunotherapy may be resumed once AE ≤1

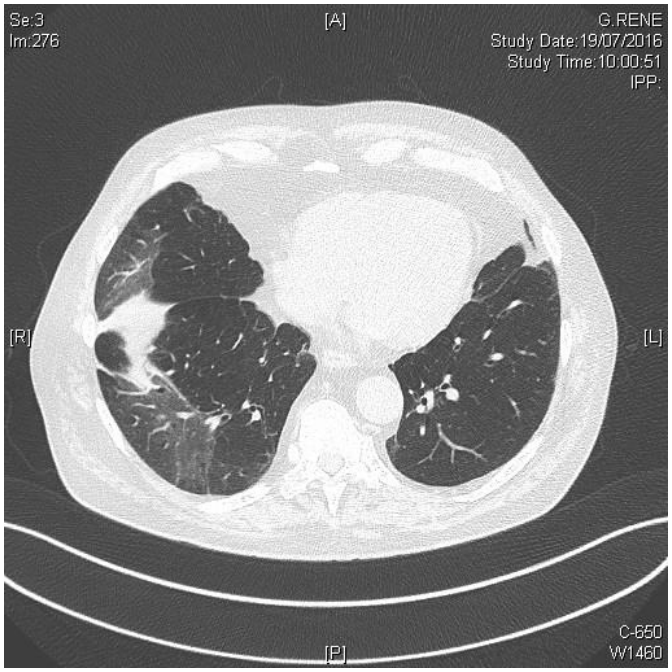
- Grade 3
  - Withhold immunotherapy
  - Consider lung specific investigations (e.g. BAL, biopsy)
  - Investigate and treat infection
  - Intravenous steroids (typical dose 1–2 mg/kg MP)
  - If not resolving within 48 h consider addition of other immunosuppressants (e.g. infliximab 5mg/kg, mycophenolate (500-1000mg/bid), or cyclophosphamide)
  - Consider restarting if toxicity grade $\leq$1 on individual basis
  - Steroids will need to be tapered over 3–6 weeks
- Grade 4
  - As for grade 3 but permanently discontinue IT

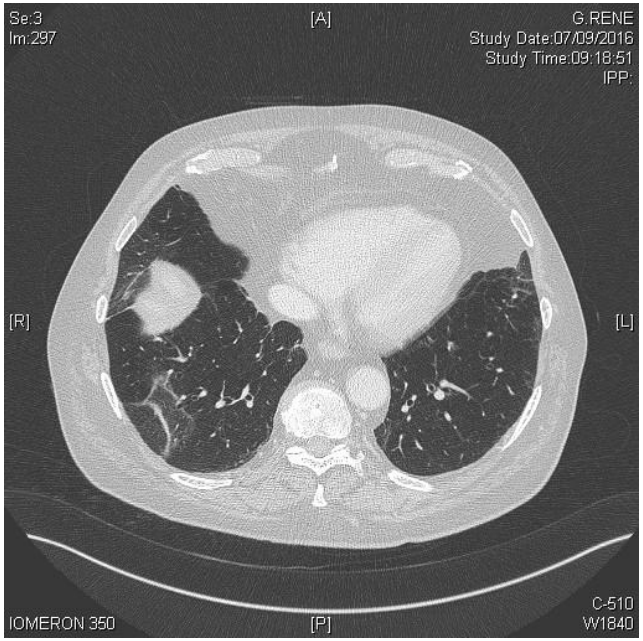
Time to improvement/resolution with steroids

- Detectable response within 3 days (Eigentler *et al*. 2016)
- Nivolumab: 3.3 weeks
- Ipilimumab + nivolumab: 6.1 weeks




Se:5
Im:260
[A]
G.RENE
Study Date:10/05/2016
Study Time:14:40:45
IPP:
[R]
[L]
IOMERON 350
[P]
C-510
W1840


Se:3
Im:276
[A]
G.RENE
Study Date:19/07/2016
Study Time:10:00:51
IPP:
[R]
[L]
[P]
C-650
W1460


Se:3
Im:297
[A]
G.RENE
Study Date:07/09/2016
Study Time:09:18:51
IPP:
[R]
[L]
IOMERON 350
[P]
C-510
W1840

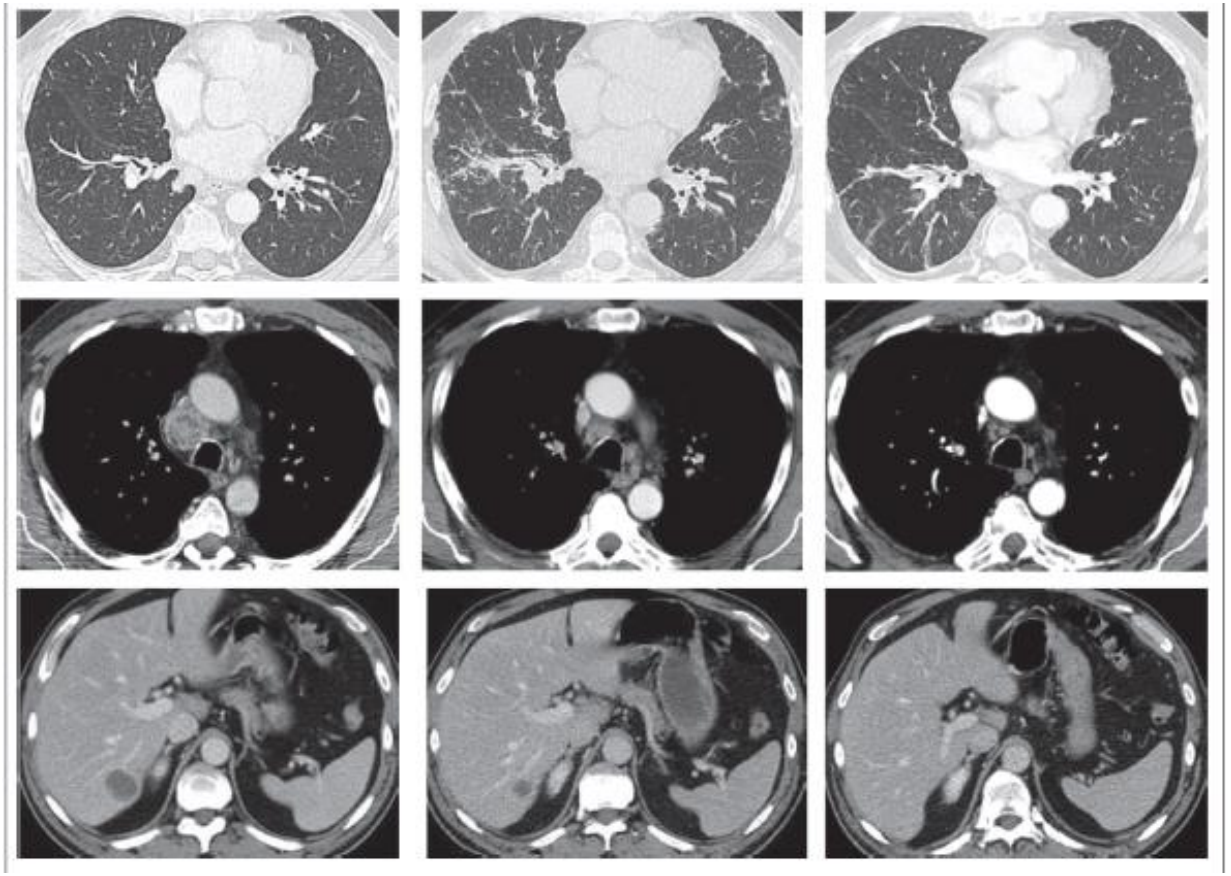
Consider

- Possible toxicity on other organs
- Infection preferentially in patients on CS or infliximab (OR 4.7-7.7)
- >80% of patients will improve/normalize
- Pulmonary IRAE may disappear despite drug continuation
- May relapse during or after steroid taper
  - Leading to uncontrollable respiratory failure
- Development of IRAE may correlate with drug efficacy and translate intro improved outcomes
- Costicosteroids seem not to adversely affect

Sarcoid-like reactions

- Ipilimumab
- Nivolumab
- Pembrolizumab

- Intrathoracic
- Extrathoracic



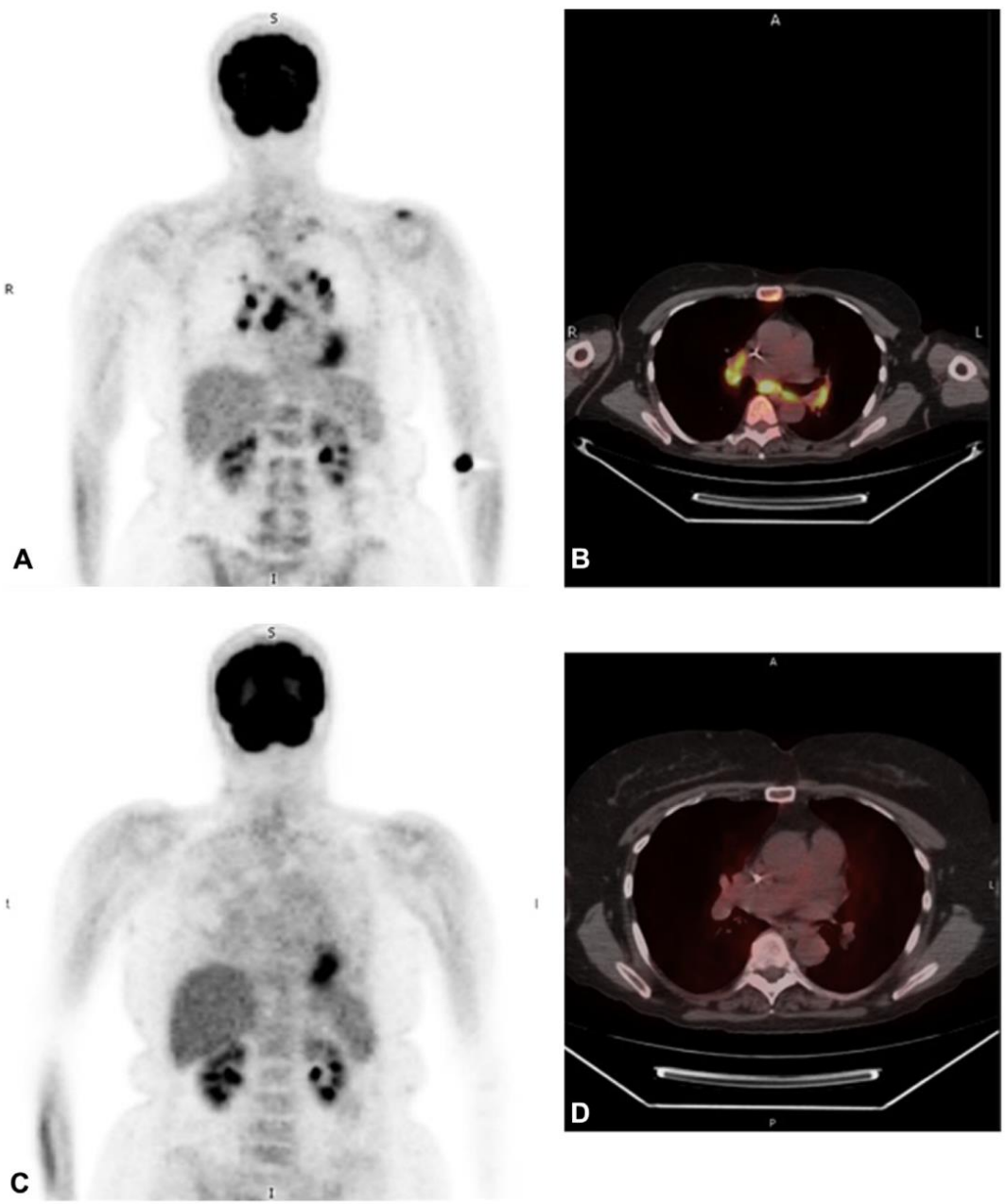
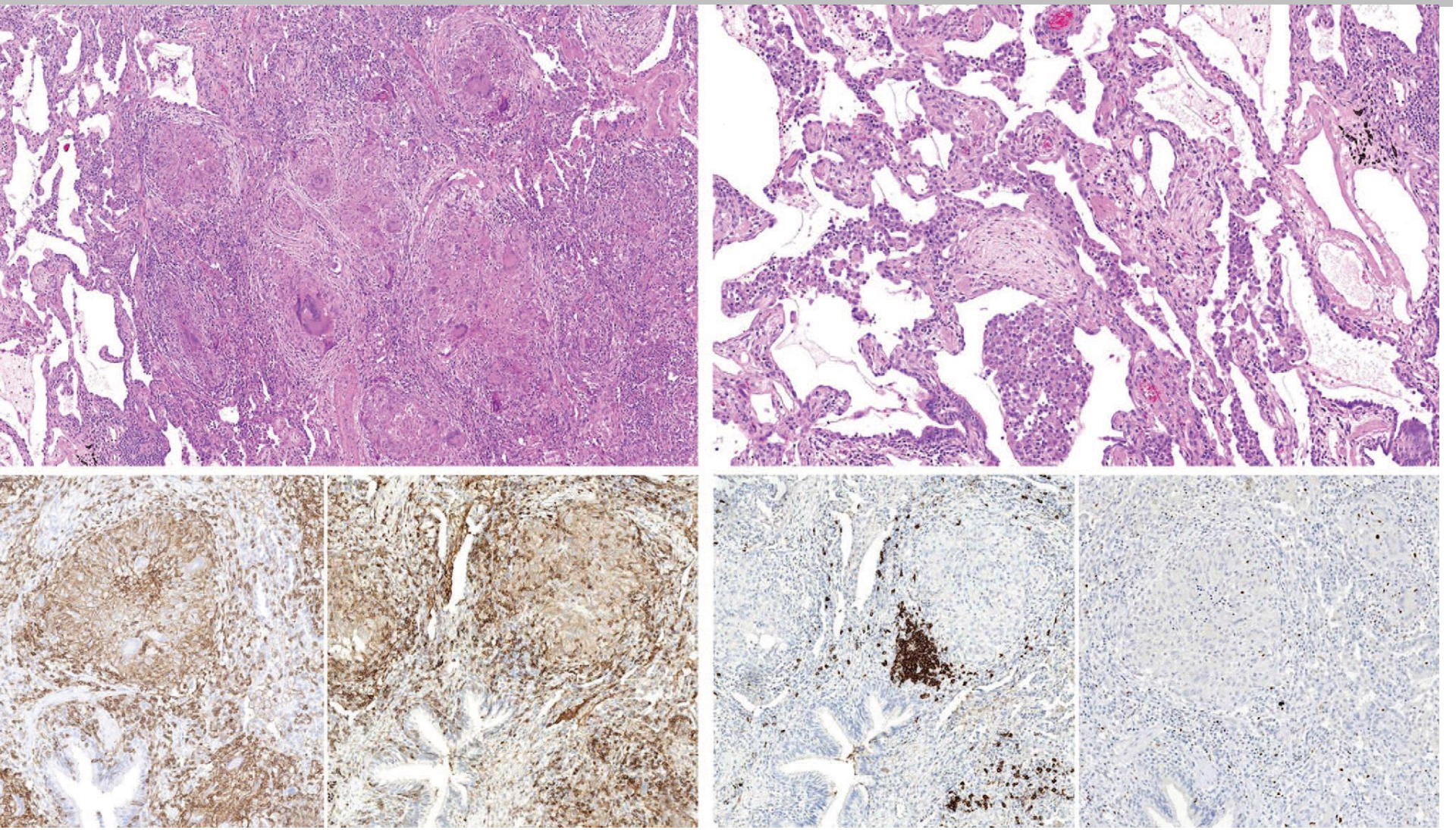


Fig 3. Radiographic examination. Positron emission tomography while taking pembrolizumab shows uptake within left scapula (**A**), sternum, hilar/mediastinal lymph nodes (**B**). Resolution of left scapula lesion (**C**), sternal lesion, and adenopathy (**D**) while not taking pembrolizumab during prednisone course.



PD1 PDL1 CTLA4 cardiotoxicity

- Heinzerling *et al*. 2016: eight cases
  - 1-Myocarditis-cardiomyopathy
  - 2-Cardiomyopathy Pw:23 mmHg
  - 3-Myocardial fibrosis (fatal)
  - 4-Reduced LVEF: 35%
  - 5-Cardiogenic shock
  - 6-Myocarditis (fatal)
  - 7-Cardiac arrest
  - 8-Myocarditis (fatal)
- Pleural effusion in pt1

Cost issues

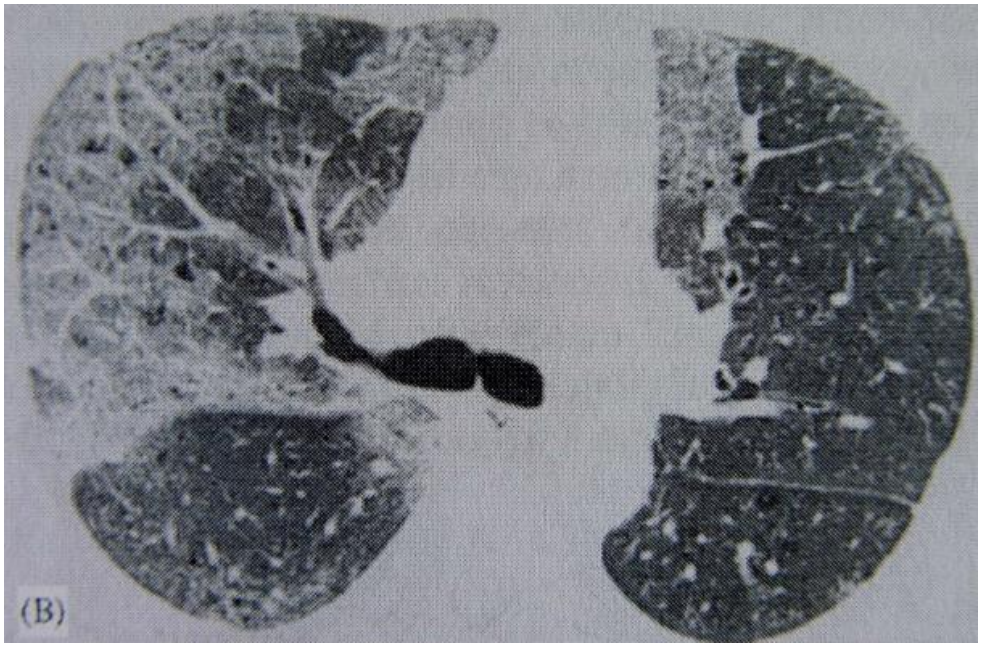
Table 5 Inpatient Costs of Treating Grade 3/4 Events Associated with Metastatic Melanoma Treatment

Adverse event	Hospitalizations per event, N	Length of stay, days			Cost, $		
		Mean	Median	SD	Mean	Median	SD
Acidosis	20	6.0	5.5	2.8	26,648	25,297	12,719
Acute kidney failure	115	7.3	5.0	9.9	31,213	20,449	41,173
Acute myocardial infarction	8	10.1	9.0	8.3	47,069	55,031	29,716
Anemia	31	3.7	3.0	2.3	19,122	19,570	10,803
Cellulitis	56	5.8	4.0	4.5	17,230	12,333	13,344
Colitis/diarrhea	10	4.5	3.0	5.6	26,861	21,290	27,690
Coma	100	5.3	4.0	4.2	31,682	23,702	26,743
Cutaneous squamous-cell carcinoma	10	4.5	1.5	5.9	25,091	21,738	19,941
Dyspnea	11	3.1	1.0	3.0	13,588	10,714	11,335
Elevated liver enzyme	7	7.7	4.0	8.9	19,122	12,344	15,127
Fever	5	3.8	3.0	1.9	15,438	13,976	7427
Hyperglycemia	21	4.3	2.0	5.2	15,827	14,478	8566
Hypertension	89	4.2	2.0	6.3	20,349	17,190	13,875
Hyponatremia	34	5.0	4.0	3.8	22,124	12,049	17,637
Hypotension	9	5.0	4.0	4.1	25,889	24,308	18,769
Nausea/vomiting	8	3.1	2.5	2.4	14,043	11,152	8724
Neuropathy	5	6.8	5.0	7.7	29,669	12,322	44,624
Oliguria/anuria	9	4.3	5.0	1.1	20,874	23,740	5053
Pneumonitis	11	9.4	5.0	7.0	28,330	21,513	22,513
Psychosis	9	5.7	4.0	6.7	13,078	11,304	9717
Rash	5	2.6	3.0	1.1	14,674	12,375	10,587
Sepsis	47	8.7	6.0	8.5	35,172	23,384	33,027
Thrombocytopenia	27	5.3	5.0	3.4	22,856	21,621	13,496

SD indicates standard deviation.

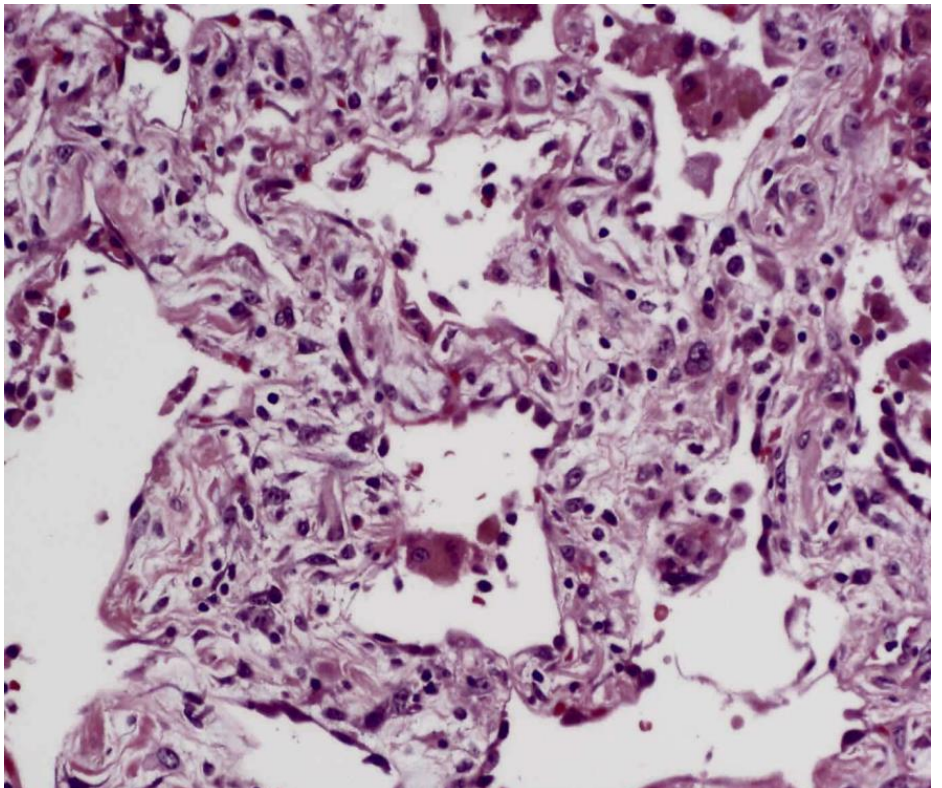
Gefitinib

- TK-*i* EGFR CBP EGFR+
- Japon 1.9% - 4.6% (1.5% mortels)
- PnI préexistante: OR 4.8-25.3
- Hors Japon: 0.3%
  - NS *vs*. temoins
- Anatomie-pathologique
  - DAD
  - PIA
  - HAD



Erlotinib

- TKI HER1/EGFR
- Japon
  - 3.3%-4.2% (<75 ans), 5.1% (>75 ans)
  - Asie non Japon 1.2%
  - West: 1%
- Qq réponses corticoïdes+



Rituximab

4

When the drug is used in combination with chemotherapy drugs including bleomycin which can also cause respiratory problems, the respective role of each drug in causing the reaction is difficult to evaluate (PMID 15857843). When used as a solo agent for instance to treat connective tissue disease, rituximab can cause lung reactions on its own. Rituximab also exposes to the risk of pneumocystis pneumonia, which can be prevented (PMID 22157468, 23258406)

Last update 22/12/2013

Patterns

I.a	Acute pneumonitis/ILD	2
I.b	Subacute pneumonitis/ILD	2
I.d	Organizing pneumonia (OP/BOOP)	2
I.g	Pulmonary fibrosis	1
I.l	Diffuse alveolar damage (DAD)	2
II.a	Pulmonary edema, noncardiogenic (NCPE)	2
II.b	ARDS	2
II.i	Flash (fulminate) pulmonary edema	1
III.a	Diffuse alveolar hemorrhage	1
III.c	Hemoptysis	1
IV.c	Obliterative bronchiolitis see also IVn)	1
IV.f	Catastrophic / fatal bronchospasm	-
X.b	Antiphospholipid antibody syndrome	1
X.f	Anaphylaxis - Anaphylactoid reactions	1
X.g	Hypersensitivity-, infusion reactions	3
X.k	Sarcoid-like thoracic and/or extrathoracic disease	-
X.n	The tumor lysis syndrome (TLS)	1
X.s	Systemic ANCA-positive disease/vasculitis	1
XI.n	Neutropenia, agranulocytosis, sepsis	2
XII.g	Coronary artery disease (acute/chronic) - Myocardial infarction	1
XV.c	Path: Organizing pneumonia (OP/BOOP-pattern) (see also Id)	1
XV.j	Path: Pulmonary fibrosis (UIP-pattern)	1

Rituximab anti-CD20

- Précoce
  - SDRA, DAD, HA
  - Lyse massive CD20+
  - Corticoïdes +

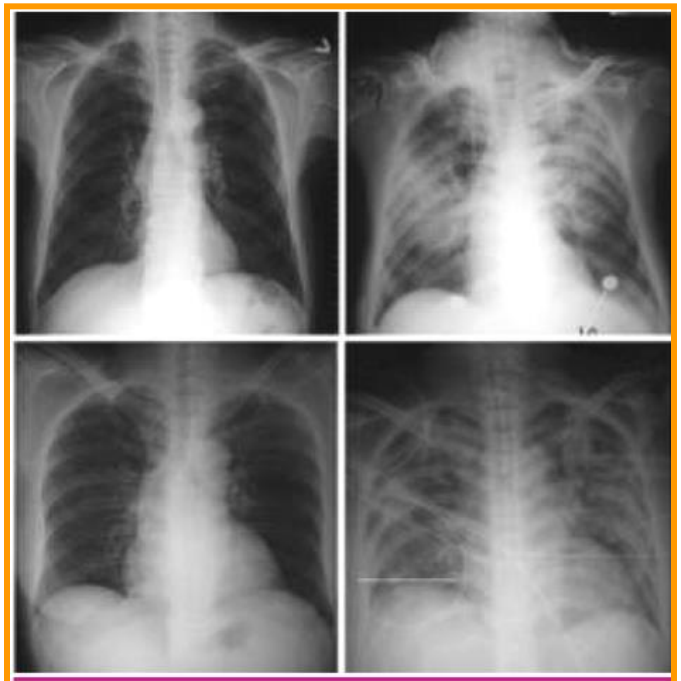


Figure 1. The chest X-ray before (left) and after (right) rituximab administration in case n. 2 (upper) and case n. 3 (lower). The post-rituximab chest films showed newly developed infiltrations and consolidation.

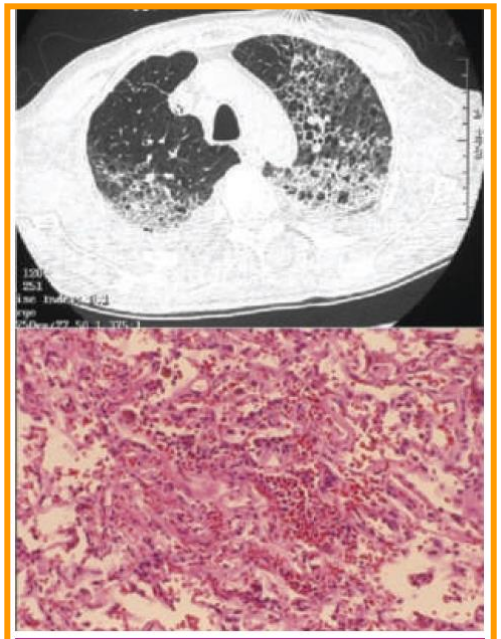
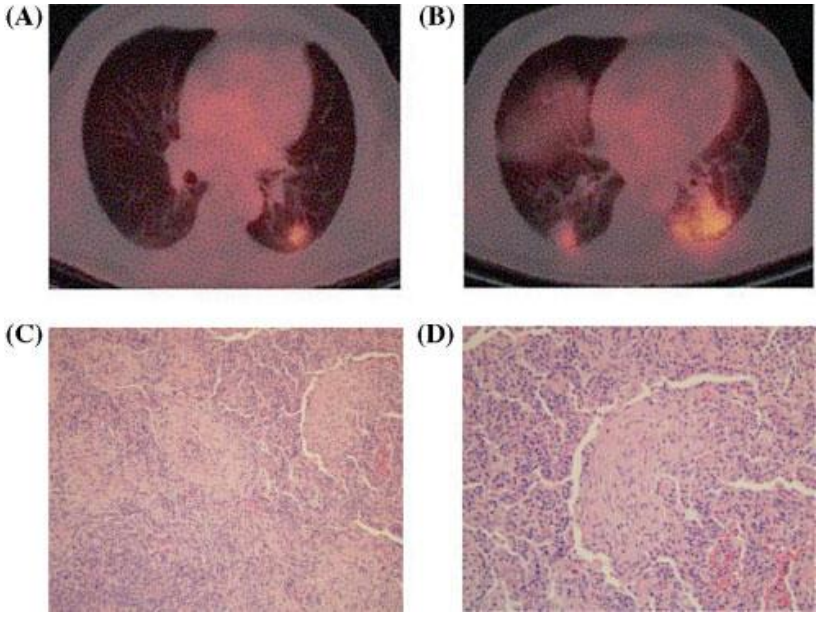


Figure 2. High-resolution computed tomography (HRCT) of the chest and histopathology of the lung biopsy tissue of case n. 2 after rituximab administration. The HRCT (upper) showed ground-glass opacity and consolidation associated with reticulation in both lungs as well as moderate bilateral pleural effusions. The diagnostic impression was interstitial pneumonitis. The histopathological examination (lower) showed pulmonary hemorrhage with an intra-alveolar proteinaceous exudate containing erythrocytes and necrotic neutrophils suggestive of acute capillaritis.

- Plus tardifs
  - BOOP cycle 4-6
  - BOOP nodulaire

- Récidive inconstante
- Mortalité: 15-18%
- *Pneumocystis …*



- Thalidomide
  - MTE
  - PnI réversible
- Lenalidomide
- Bortezomib
  - Japon OR x15

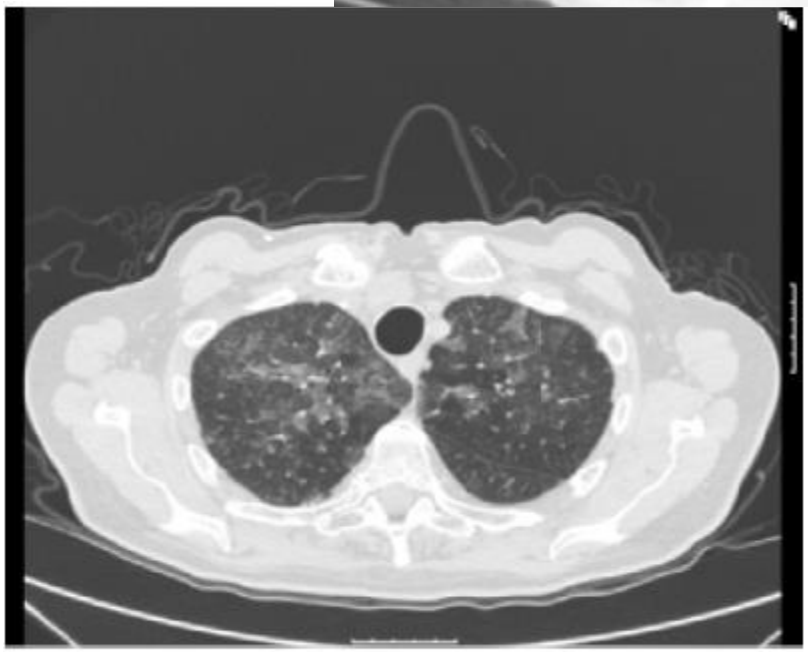


Fig. 1. Ground-glass opacities in both upper lobes and the lingula.

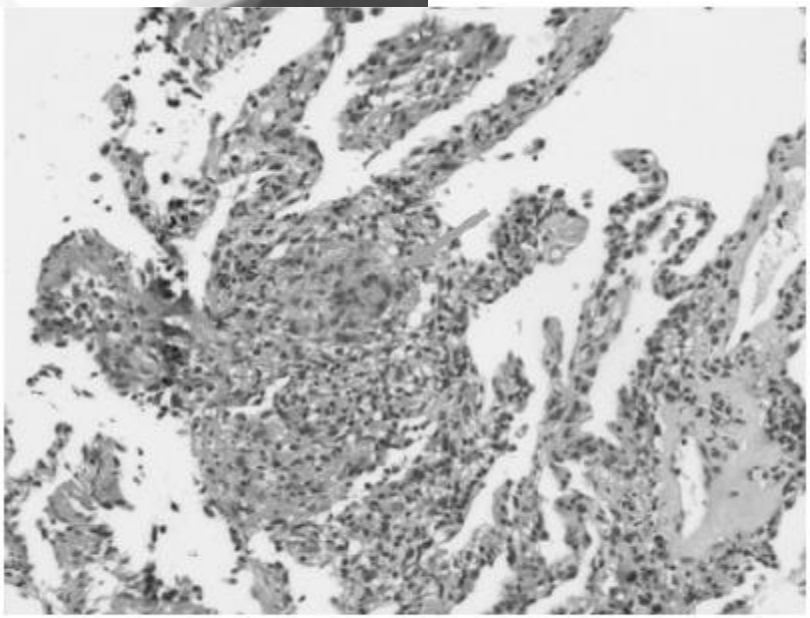
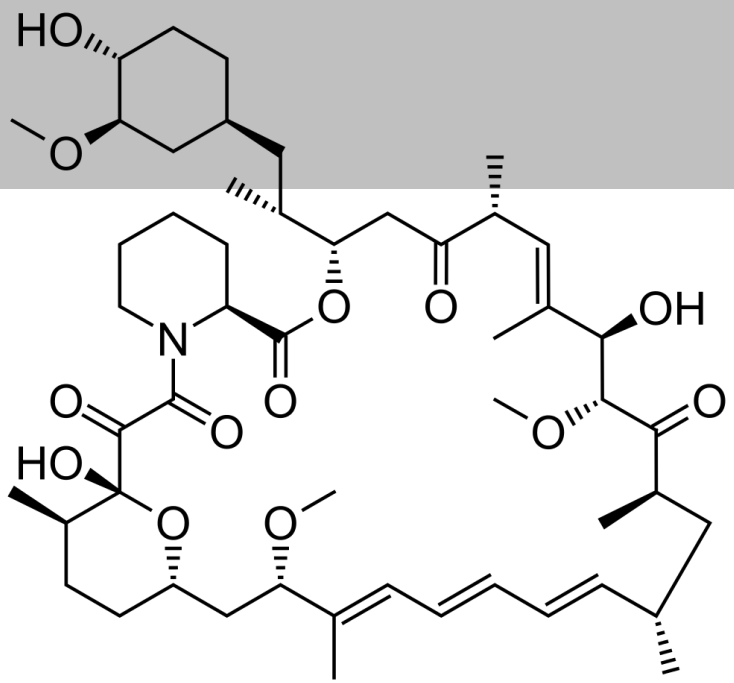
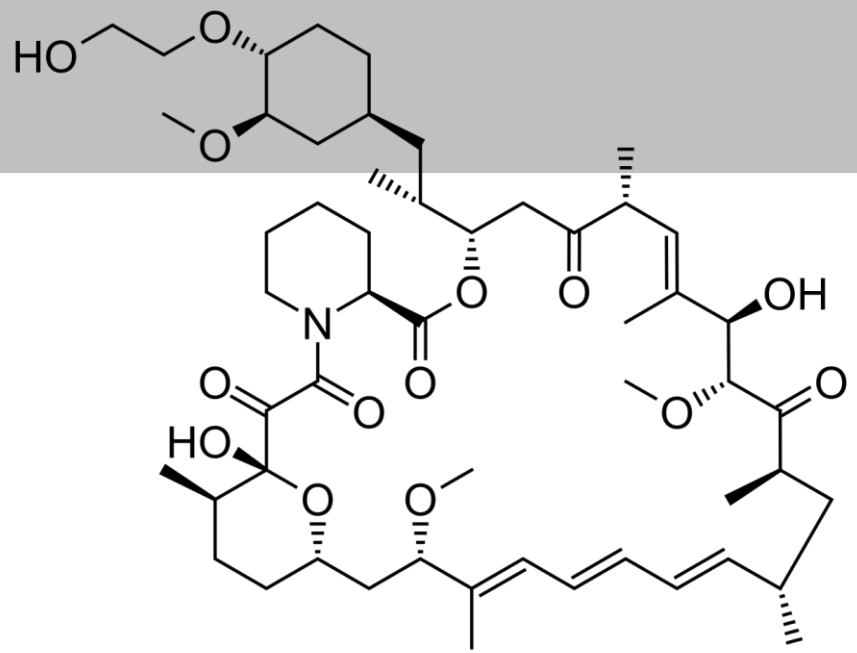


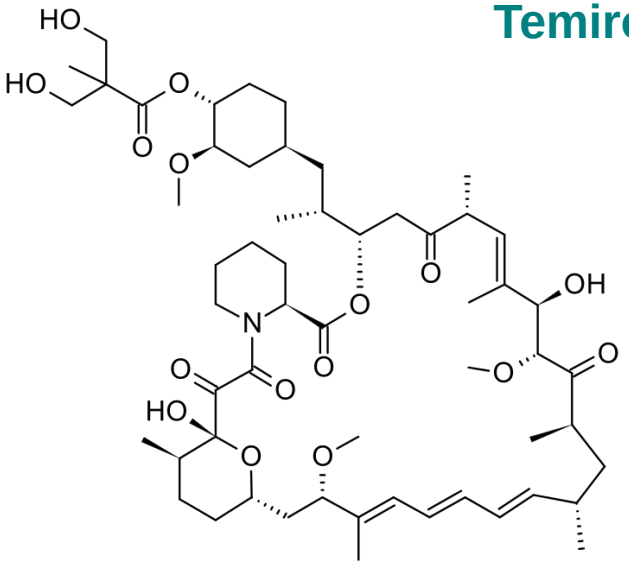
Fig. 2. Hematoxylin/eosin (HE) staining of transbronchial biopsies with lymphohystiocytic interstitial inflammation and granulomatous features (arrow).

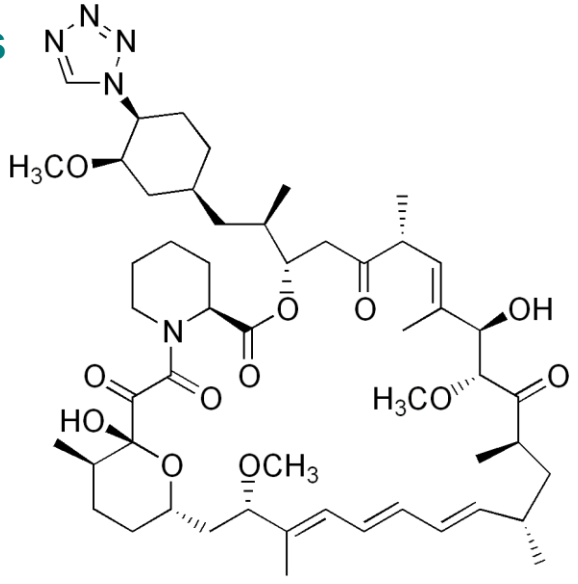




Sirolimus **Everolimus**

Temirolimus **Zotarolimus**

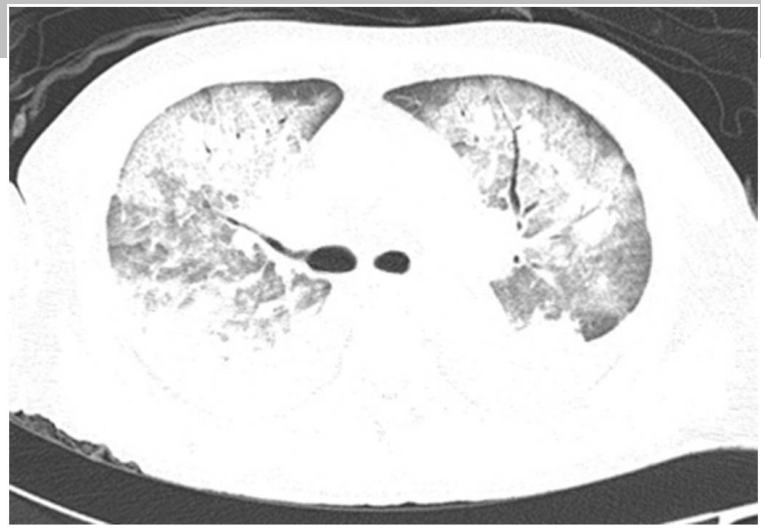




I-mTOR

- ‘PnP non-infectieuse’
- Tous pays - Toutes indications
  - Tx, CBP, RCC, LAMM
- Incidence:
  - Tx: 4-13%
  - RCC: 10-53% M: 25%
  - CBP: 24%
- M: 16 semaines, la plupart <400 j

- Symptomatiques 33%
  - Dyspnee, toux, fievre
  - Sevères 10%
- LBA
  - Ly: 80% (0-75%)
  - Eo: 12% (0-14%)
  - HA: 8%
- Mortalité 0-2%



Ana-Path

- NSIP
- LIP
- BOOP
- HA
- Granulomes

- *DIP*
- *PAP*
- *Vasculaire*

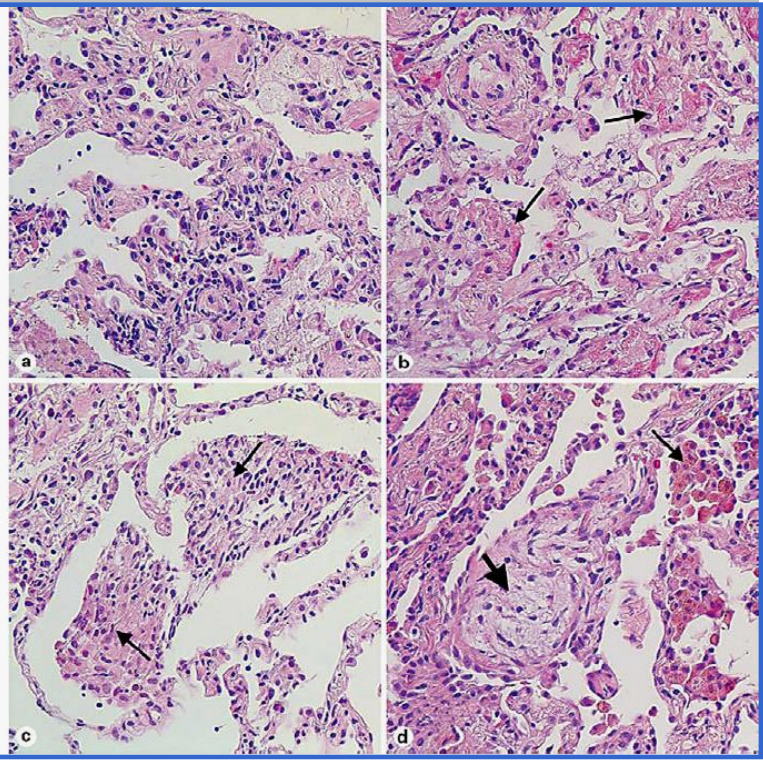


Fig. 1. a Interstitial lymphoplasmocytic inflammation (patient GC); **b** alveolar damage with fibrinous exudates (arrows; patient GC); **c** intraalveolar epithelioid granulomas (arrows; patient RW); **d** pattern of organizing pneumonia with intraalevolar polyploid plug of organizing connective tissue (small arrow). Hemosiderin-loaded macrophages (large arrow; patient RW). HE. ×200.

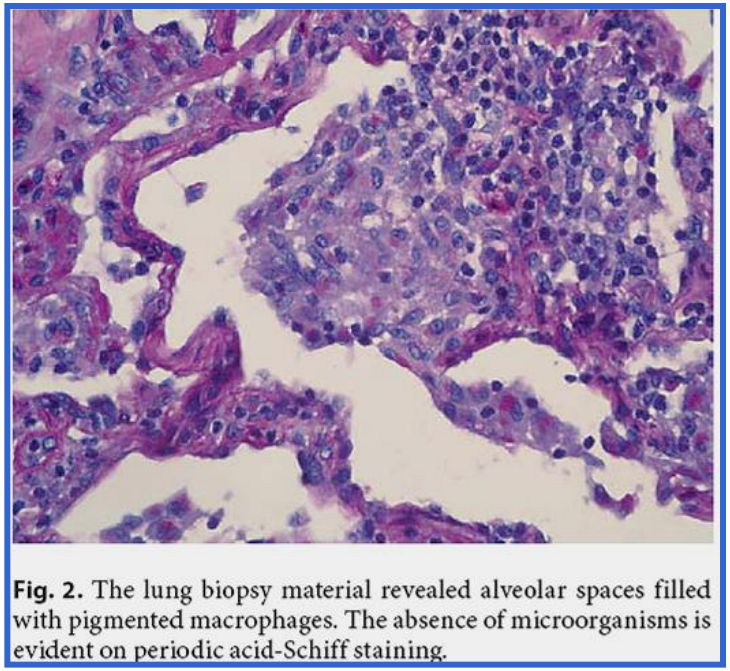
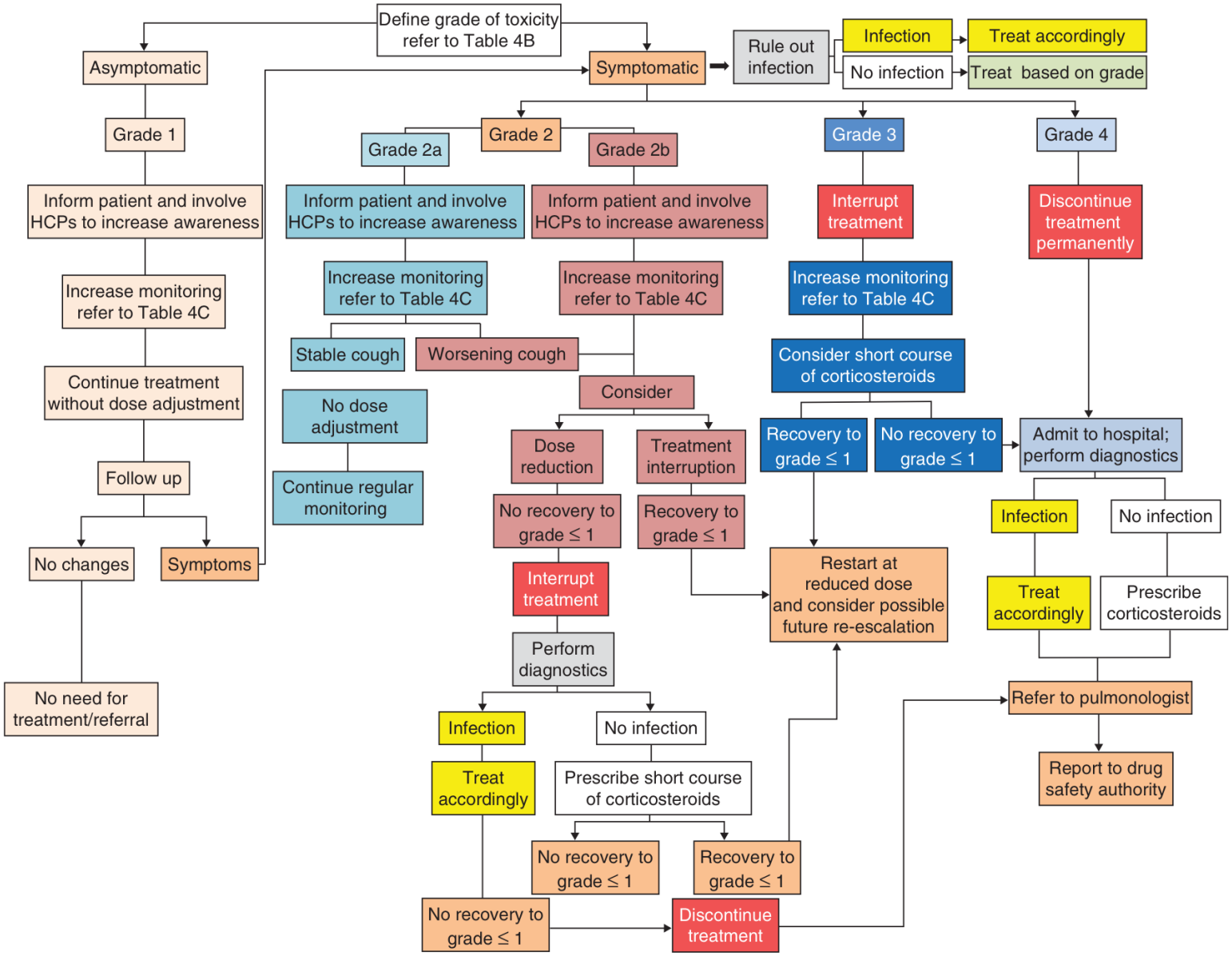
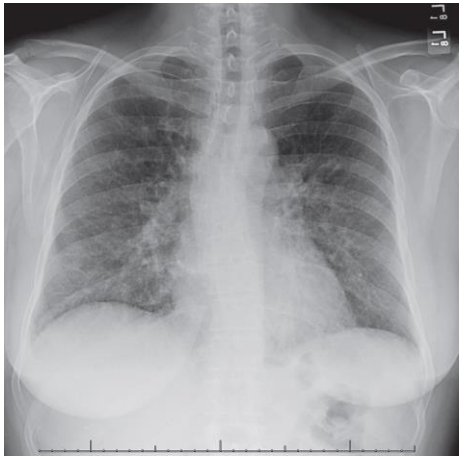


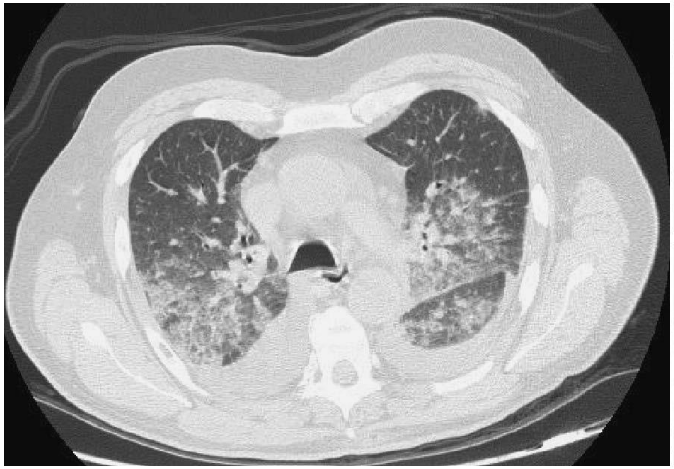
Fig. 2. The lung biopsy material revealed alveolar spaces filled with pigmented macrophages. The absence of microorganisms is evident on periodic acid-Schiff staining.

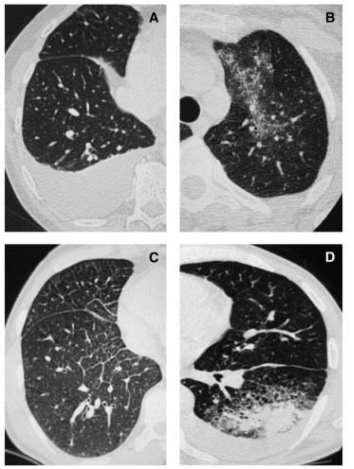
- Dose - posologie
- Réduction ou éviction selon gravité
- Réadministration: 65%
- PnI: pronostic favorable?
  - mRCC
  - Médiane
    - Pneumopathie + (28): 594 jours
    - Pneumopathie - (83): 436 jours


Define grade of toxicity refer to Table 4B
Asymptomatic
Grade 1
Inform patient and involve HCPs to increase awareness
Increase monitoring refer to Table 4C
Continue treatment without dose adjustment
Follow up
No changes
Symptoms
No need for treatment/referral
Symptomatic
Rule out infection
Infection
Treat accordingly
No infection
Treat based on grade
Grade 2
Grade 2a
Grade 2b
Grade 3
Grade 4
Inform patient and involve HCPs to increase awareness
Inform patient and involve HCPs to increase awareness
Interrupt treatment
Discontinue treatment permanently
Increase monitoring refer to Table 4C
Increase monitoring refer to Table 4C
Increase monitoring refer to Table 4C
Stable cough
Worsening cough
Consider short course of corticosteroids
No dose adjustment
Continue regular monitoring
Consider
Recovery to grade ≤ 1
No recovery to grade ≤ 1
Admit to hospital; perform diagnostics
Dose reduction
Treatment interruption
No recovery to grade ≤ 1
Recovery to grade ≤ 1
Infection
No infection
Interrupt treatment
Restart at reduced dose and consider possible future re-escalation
Treat accordingly
Prescribe corticosteroids
Perform diagnostics
Refer to pulmonologist
Infection
No infection
Treat accordingly
Prescribe short course of corticosteroids
Report to drug safety authority
No recovery to grade ≤ 1
Recovery to grade ≤ 1
No recovery to grade ≤ 1
Discontinue treatment

- Imatinib
  - PnI, rétention hydrique
- Dasatinib
  - PnI
  - Ep. pleural 7-39%
  - HTAP
- Nilo-
- Bosu-
- Pona-

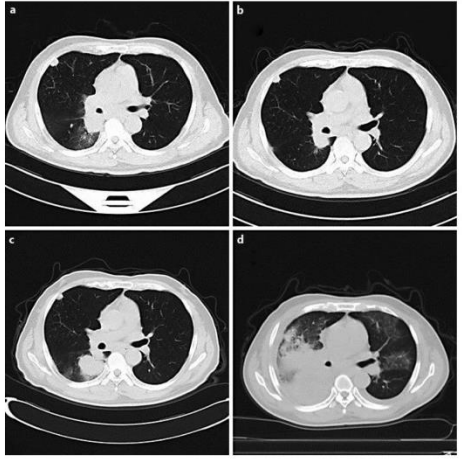


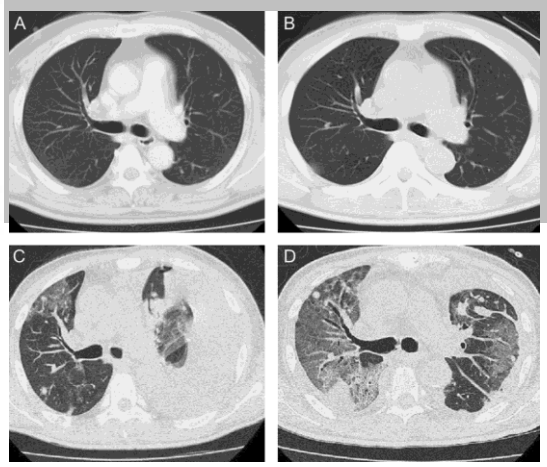




- Crizotinib
- Fludarabine
- Idelalisib
- Ibrutinib
- Azanucleosides (azacitidine, decitabine)
- Copanlisib
- Bevacizumab
- Trastuzumab: cardiopathies
- Sorafenib, sunitinib: cardiopathies
- Pazopanib

Sorafenib

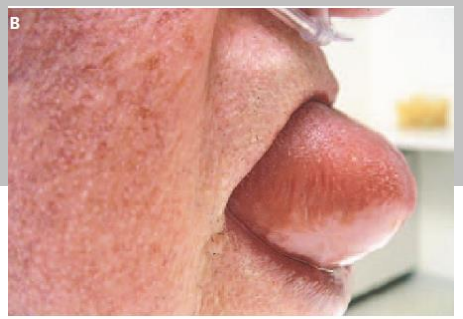




I.a	Acute pneumonitis/ILD	-
I.b	Subacute pneumonitis/ILD	1
II.b	ARDS	1
IV.a	Bronchospasm, asthma attack	1
X.n	The tumor lysis syndrome (TLS)	1
XII.a	Left ventricular dysfunction or failure	2
XVII.g	Tuberculosis	1

- Accidents non parenchymateux

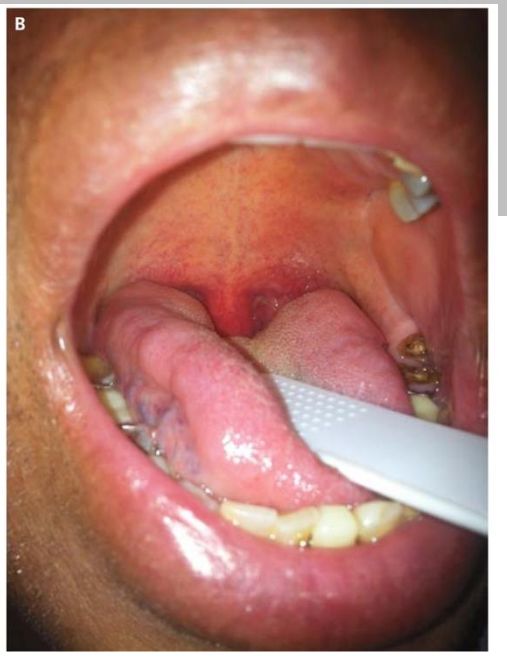
VAS



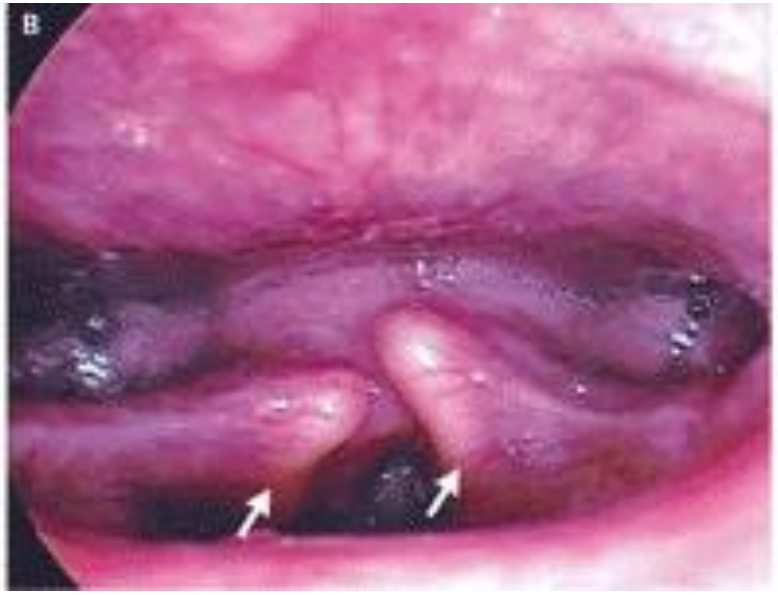
- Œdème laryngé: IEC, ARA2, bioth.
  - Sd asphyxique
  - CI à tout IEC
  - Icatibant


D


A


B


A


B

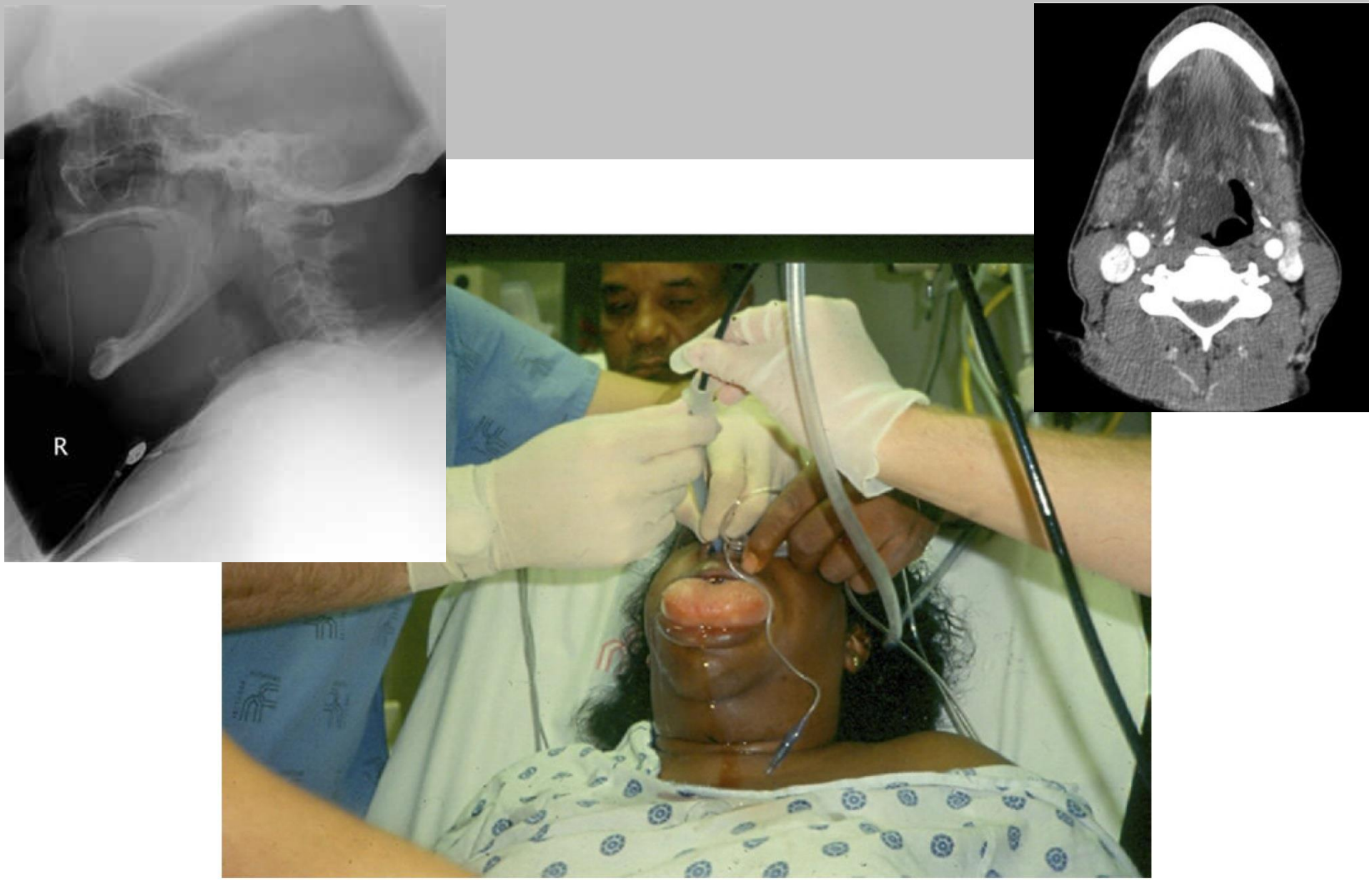
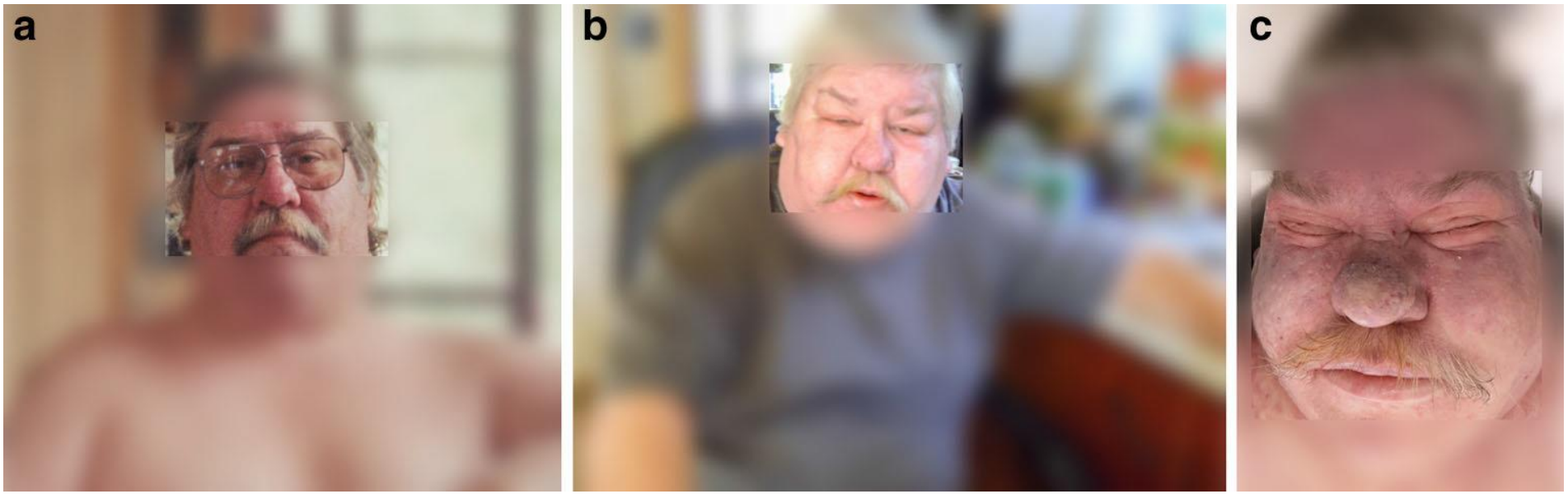


Figure 1. Example of life-threatening ACE inhibitor–induced angioedema with attempted emergency fiber optic nasotrachael intubation. The procedure was unsuccessful, and an emergency cricothyroidotomy was performed with great difficulty.


a
b
c

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

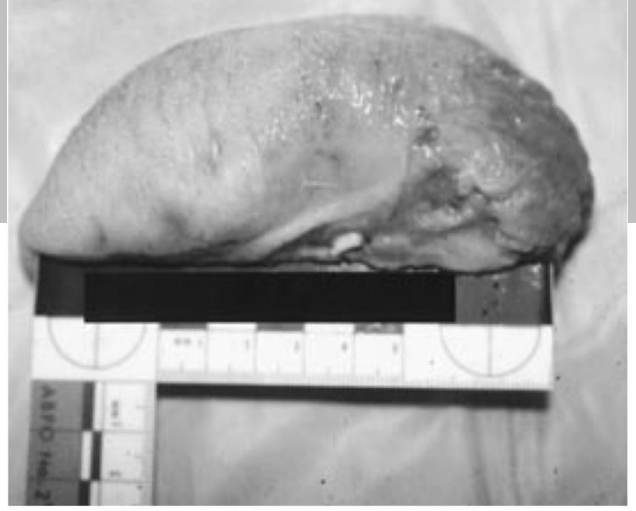
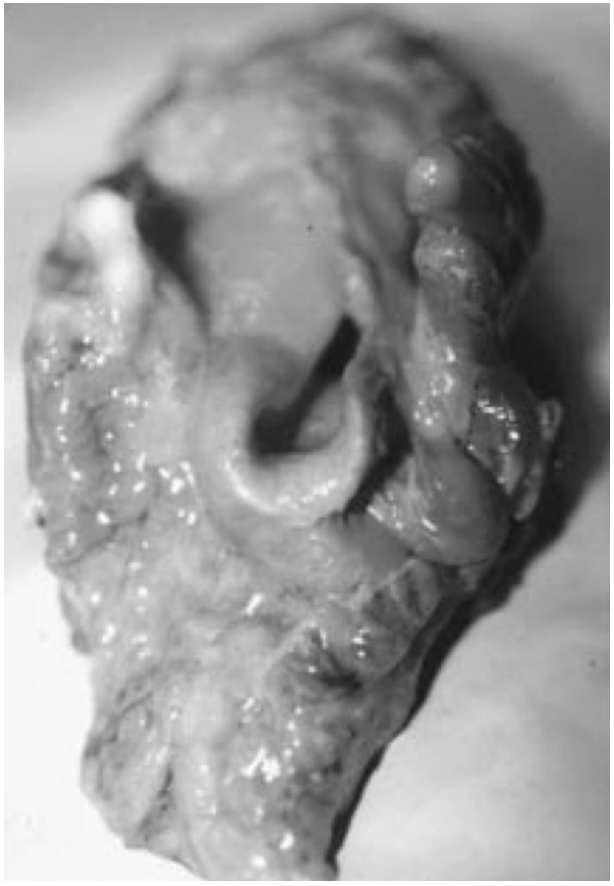


FIG. 2—*Angioedema of tongue.*



Voies aériennes

- Bronchospasme aigu/suraigu
  - AINS, B-bloqueurs, aspirine
  - Encéphalopathie postanoxique

- Toux
  - IEC, IFN
  - Eviction +++

Pill aspiration syndrome

CHEST Special Features

"Pills" and the Air Passages

Elif Küpeli, MD; Danai Khemasuwan, MD, MBA; Pyng Lee, MD, FCCP; and Atul C. Mehta, MD, FCCP

Aspiration of a medication in the airways in any form produces a variety of adverse effects, both local and systemic. Furthermore, specific reaction of the airways to each type of pill strongly affects the outcome. It is crucial for pulmonologists and emergency medicine specialists to acknowledge this clinical entity. In addition, airways have been increasingly used to deliver medications such as insulin and prostacycline. These aerosolized medications can also cause local as well as systemic side effects. We review the local and systemic reactions of these "pills" accessing the airways either by incidental aspiration or iatrogenic administration. We address clinical presentation, mechanism of injury, diagnosis, and management of complications of these pills in the air passages.

CHEST 2013; 144(2):651–660

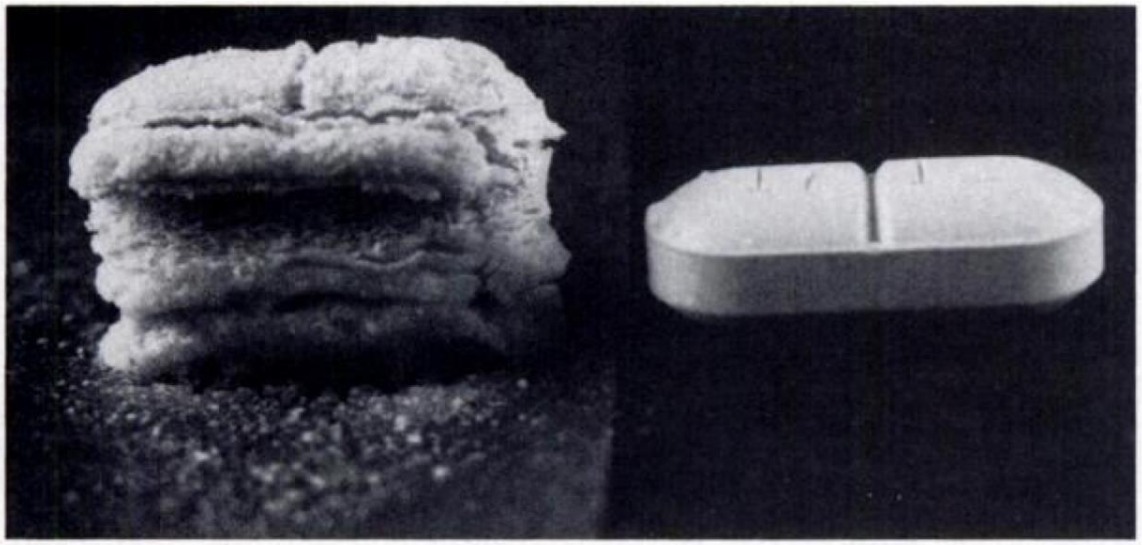


FIGURE 2. Rapid expansion of a sucralfate tablet is seen 30 s after placing it on a wet surface *(left)*, compared with a dry tablet *(right)*.

The Iron Lady

Horiana B. Grosu[1], Carlos A. Jimenez[1], Georgie A. Eapen[1], David Ost[1], Cesar Moran[1], and Rodolfo C. Morice[1]

[1]Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas

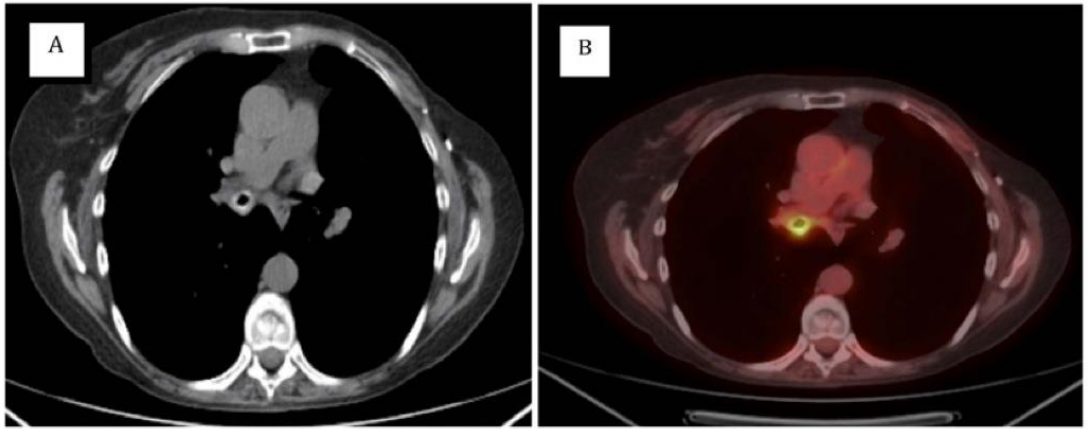


Figure 1. (*A*) Computed tomography image with circumferential thickening of the bronchus intermedius. (*B*) Positron emission tomography–computed tomography image with circumferential fluorodeoxyglucose-avid area of the bronchus intermedius.

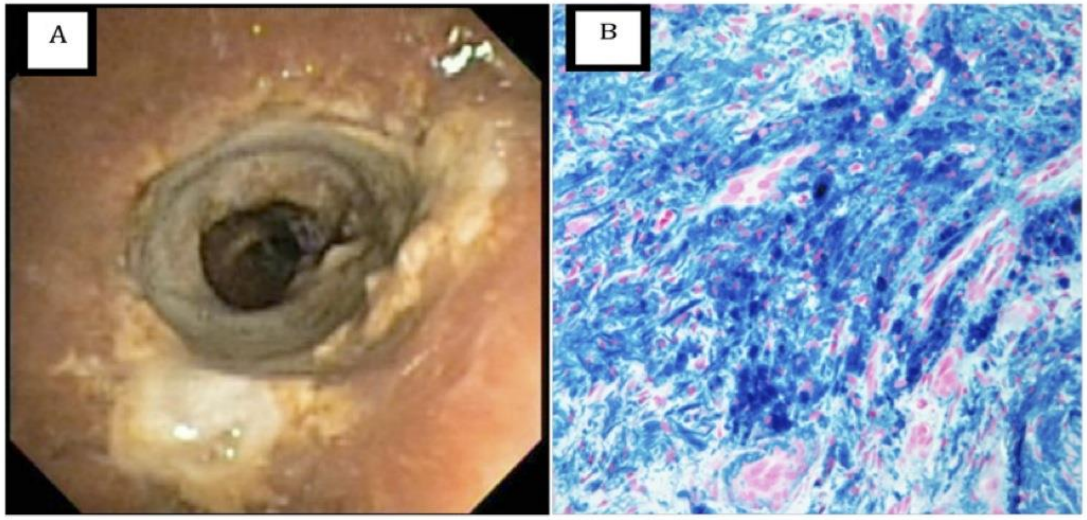


Figure 2. (*A*) Bronchoscopic view of bronchus intermedius with brown staining and necrosis of the mucosa. (*B*) Biopsy specimen showing strong positive reaction for iron.

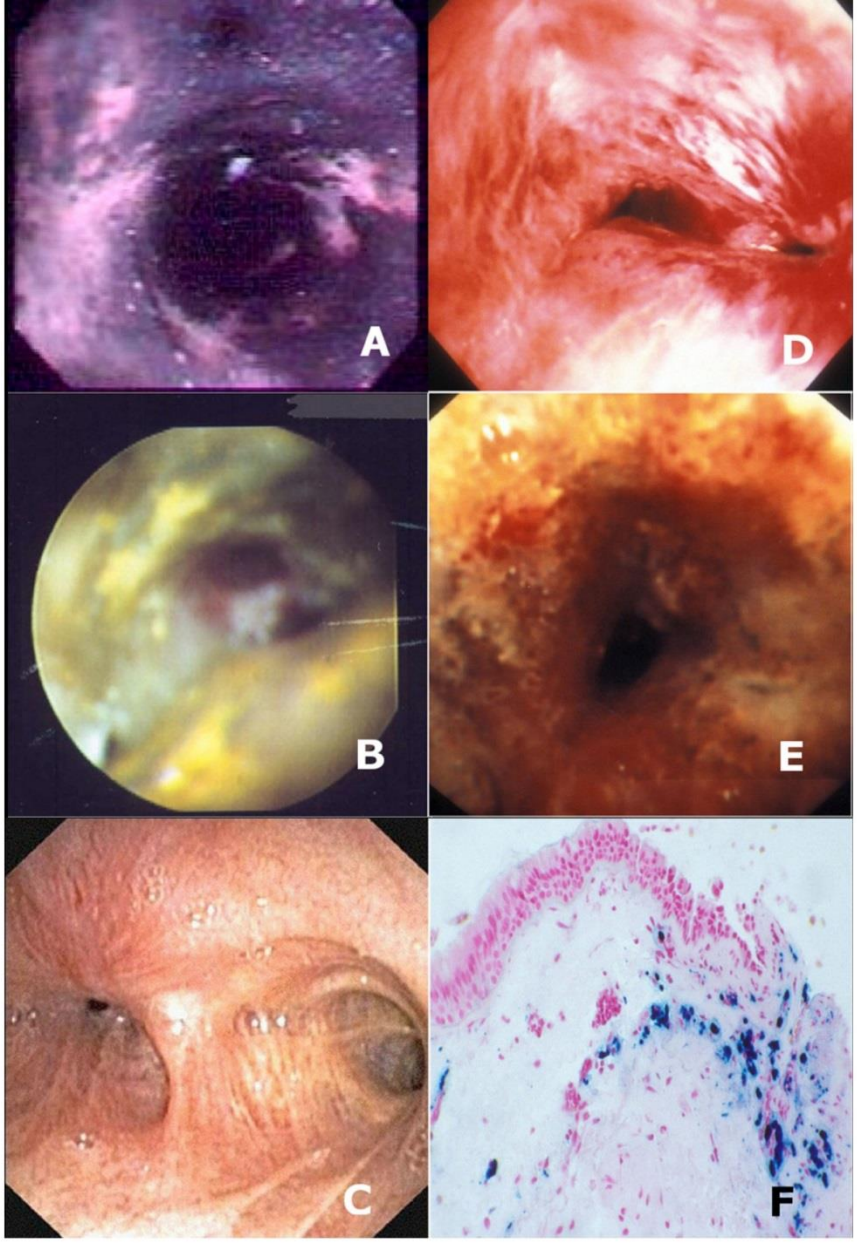
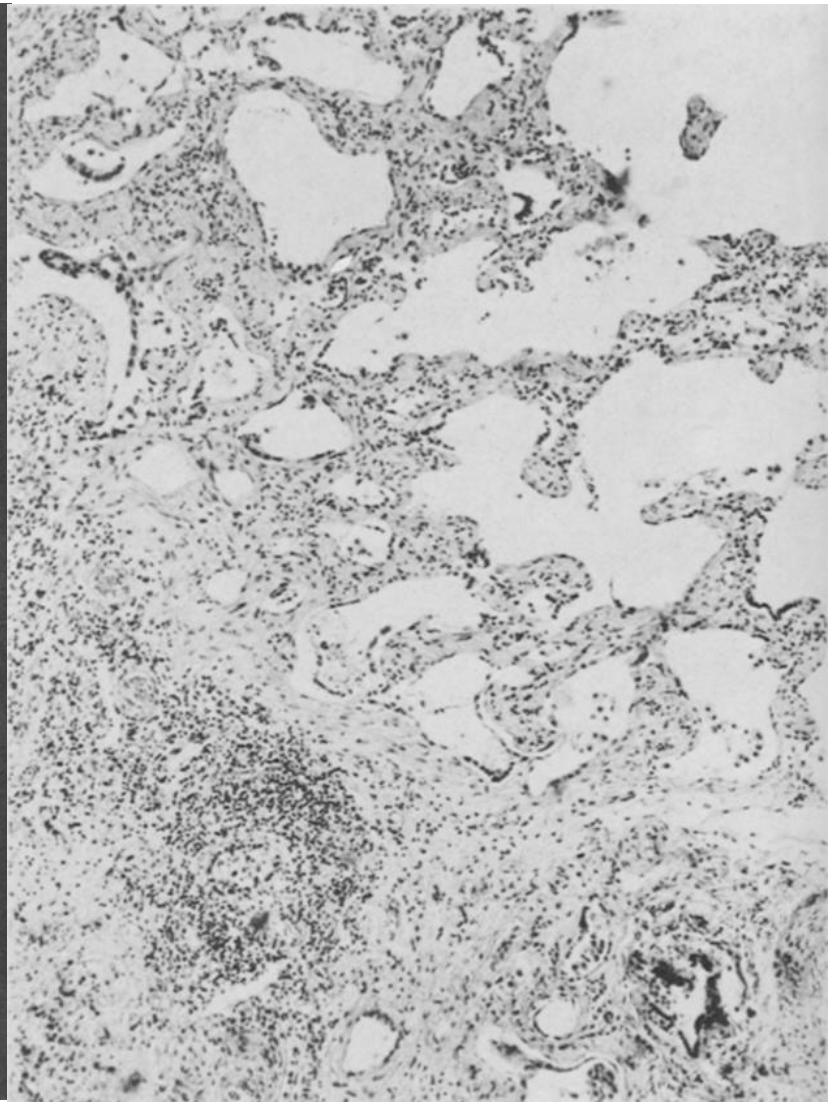
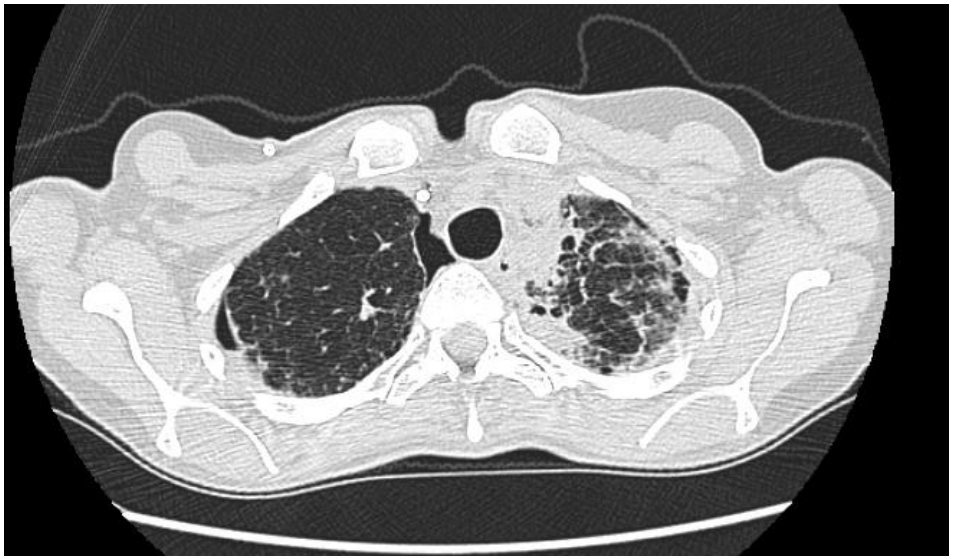


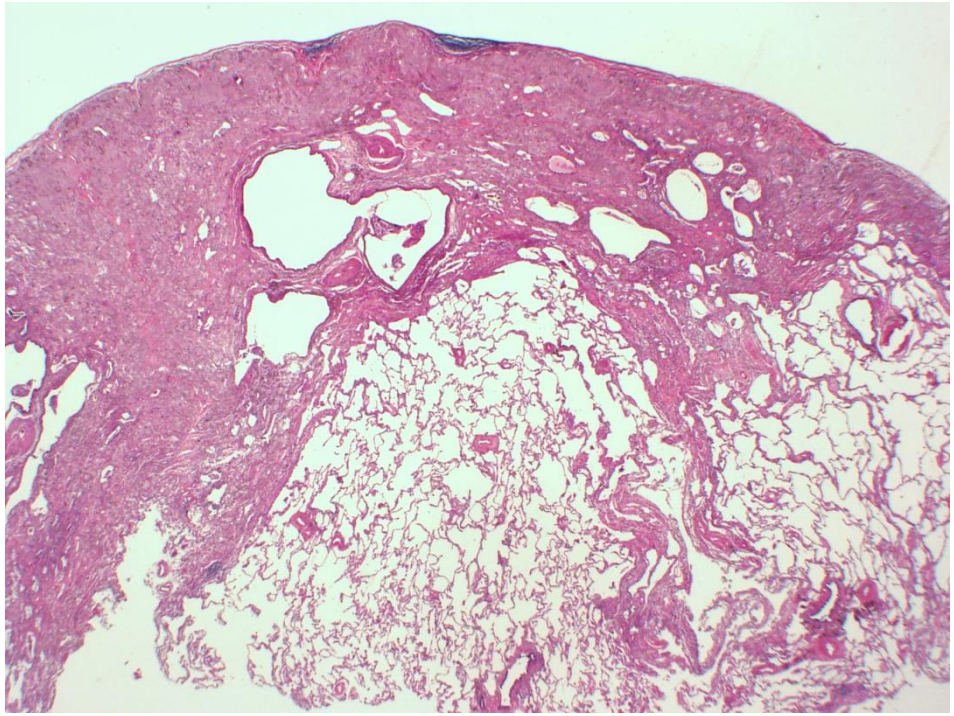
FIGURE 1. A, Charcoal in the tracheobronchial tree. (Reprinted with permission from Rajamani et al.[4]) B, Bronchus intermedius inflammation at day 1 after potassium-pill aspiration. Note, no foreign body was seen in the bronchus intermedius on day 1. C, Bronchus intermedius inflammation at 1 month after potassium-pill aspiration. (Reprinted with permission from Gudavalli et al.[11]) D, Intense inflammation of the bronchus intermedius following iron-pill aspiration. No foreign body was detected in the bronchus intermedius. E, Intense inflammation of right main stem bronchus following iron-pill aspiration. F, Endobronchial biopsy specimen revealing submucosal deposition of iron particles on Prussian blue stain (original magnification $\times 200$).

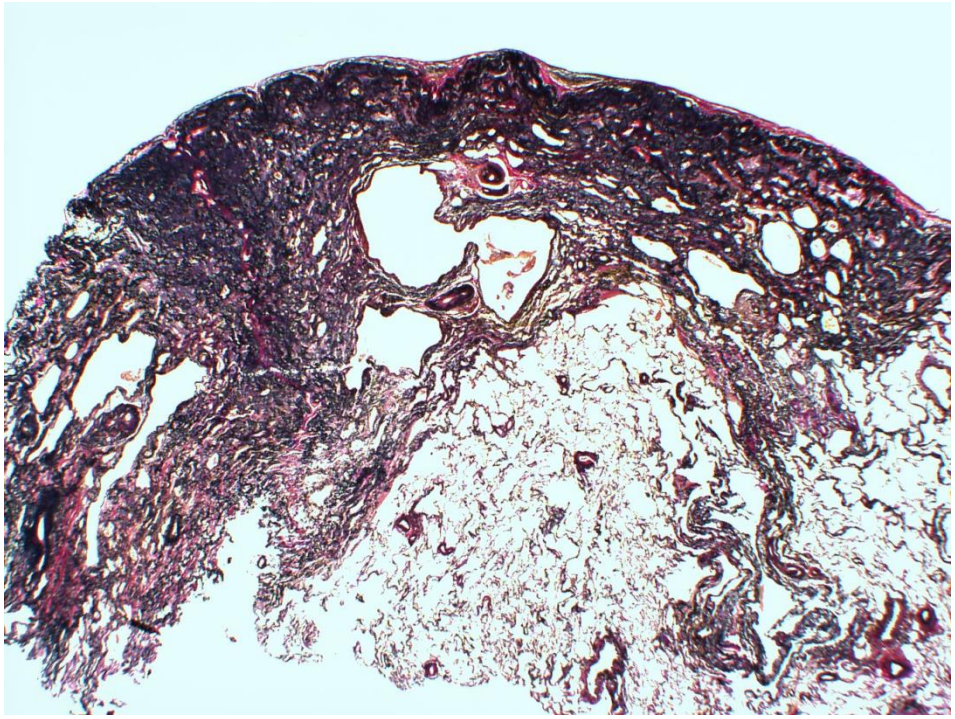
Fibro-élastose pleuro-parenchymateuse

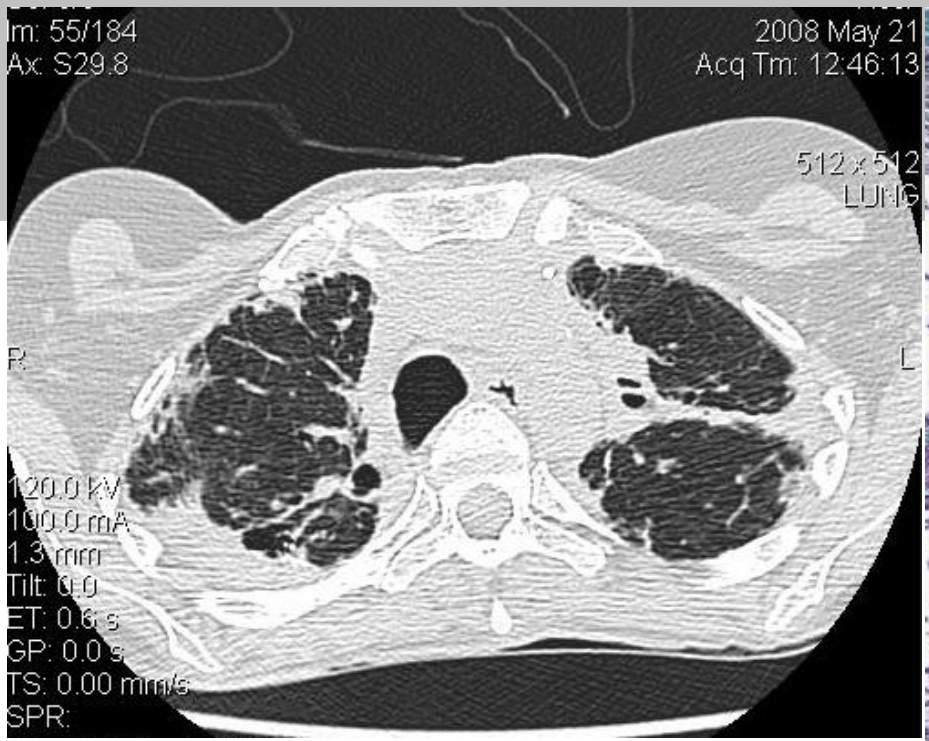


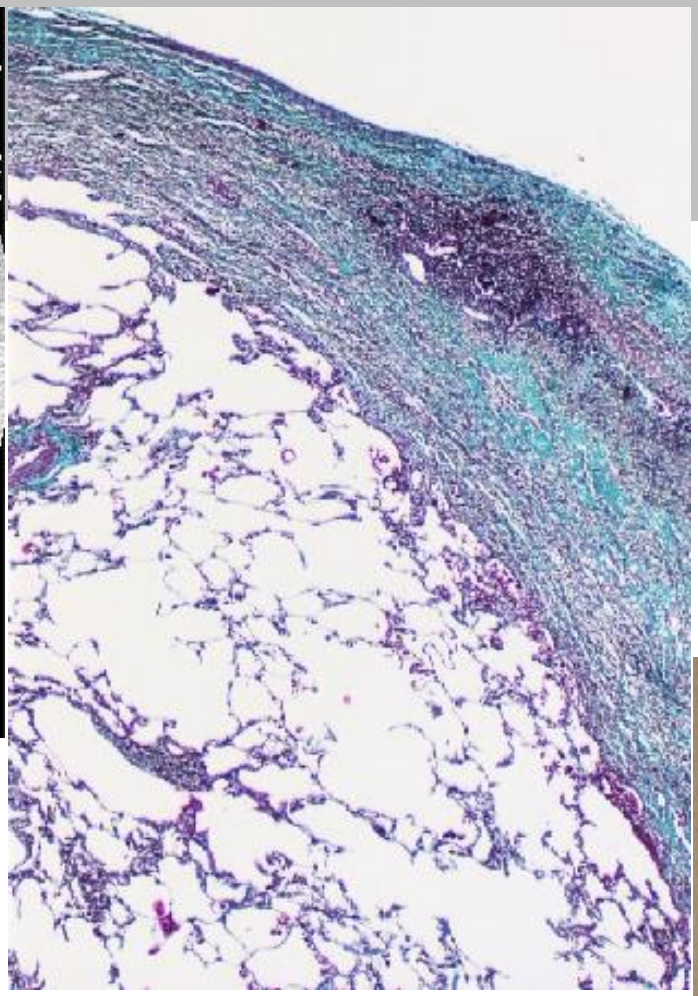

BOUSTA DJAMEL
01 NO C
2000/02/08
NETTER









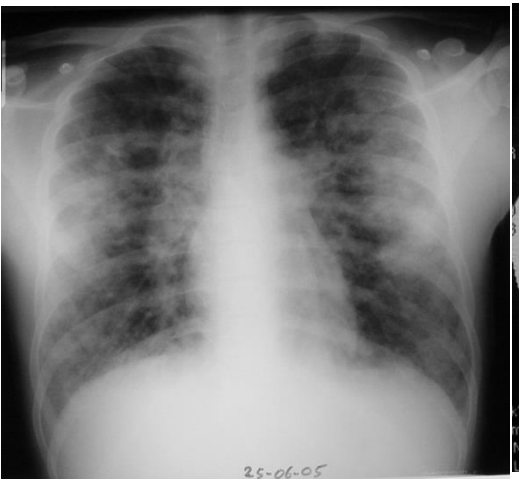


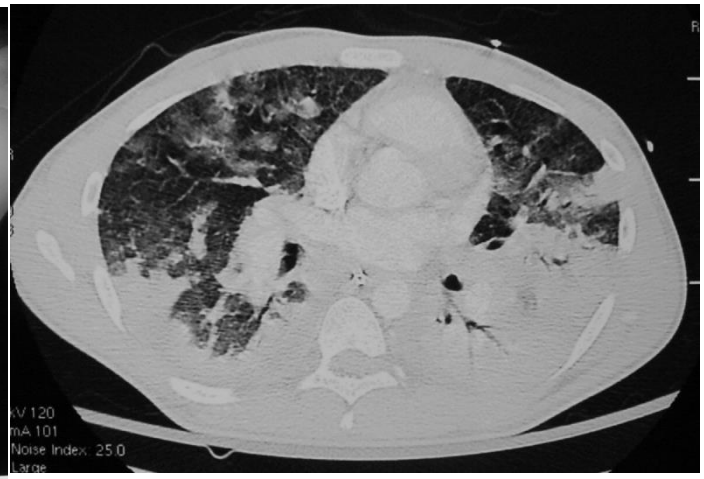
- Idiopathique
- Contexte de TCSH ou pulmonaire
- ~10% ont reçu des alkylants CPM+++
- Trois Tx pulmonaire

- Maladies de système
  - Mimes parfaits de leur équivalent idiopathique

DRESS

- Rash
- Eosinophilie
- Cytopénie, lympocytes atypiques
- Atteintes viscérales
  Rein, foie, SNC, TD, adénopathies
  myocardite
- PIE ~15%





Autoimmunité

- Infliximab – Crohn (Vermeire et al. 2003)

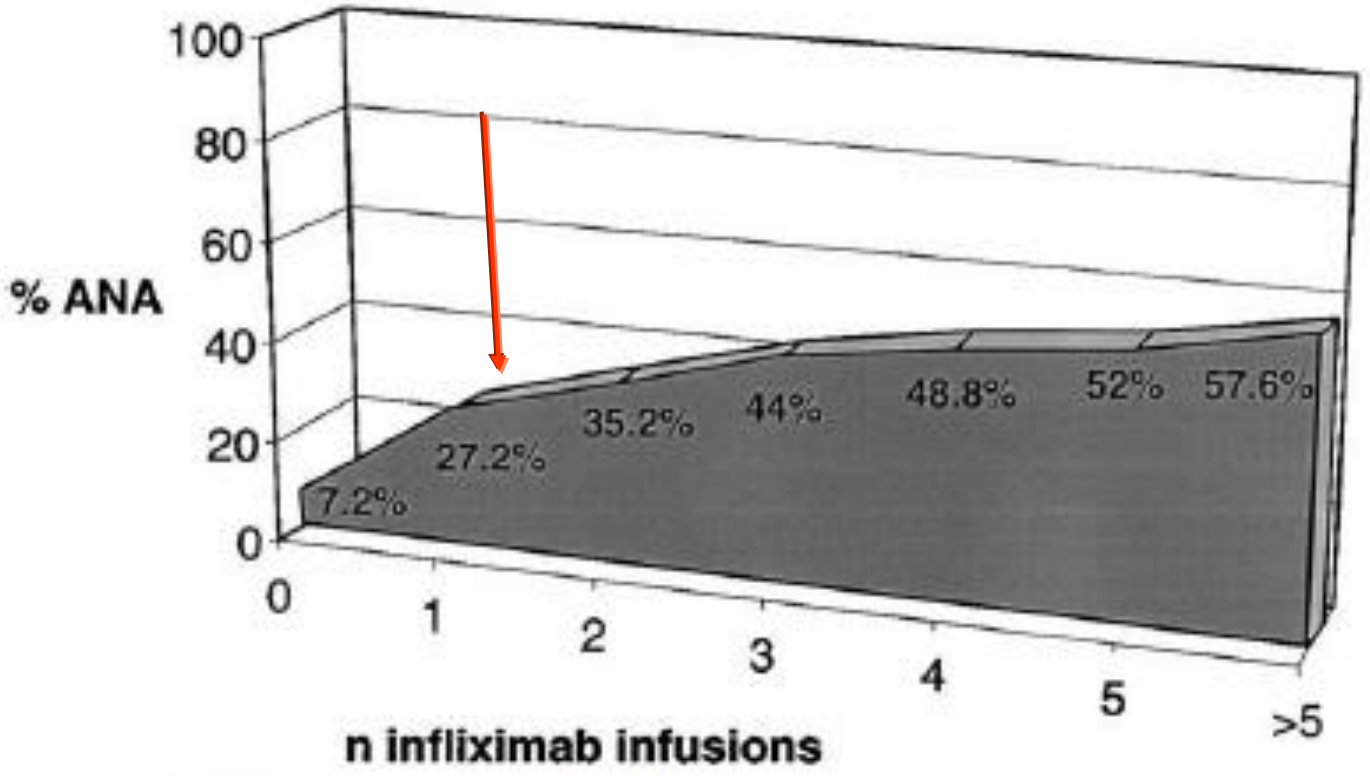


Figure 2. The relationship of ANA incidence (Y axis) with regard to the number of infliximab infusions (X axis) in the study cohort (n = 125).

- 125 patients
- Incidence AAN @ 24 mois 71/125 (56.8%)
  - ~50% > dès la 1ère administration
  - >75% avant la 3é administration
- Eviction: 15/71 redevenus seronégatifs (mediane 12 mo)
- 43 AAN sous-typés
  - 14/43 (32.6%) ant-ADN ds
  - 17/43 (39.5%) monobrin
  - 9 (20.9%) antihistone
  - 0 ENA
- Deux (antihistone + antiADNds) -> lupus clinique bénin
- Sexe féminin (OR: 3.2)

- GPA ANCA+
- EGPA
- Pseudo-sarcoidoses (Etanercept, CPI)
- Myopathies - myosites
- Vascularites ANCA+
- Dual ANCA disease
- Goodpasture anti-GBM
- CIVD
- MODS
- Propofol infusion syndrome
- *Pyoderma gangrenosum*

DI-ANCA-related systemic conditions

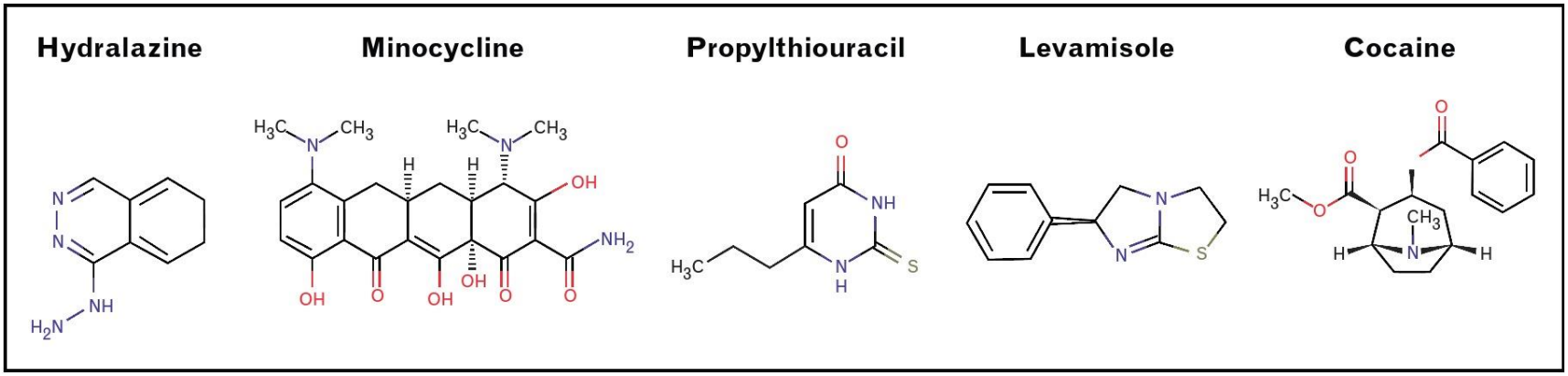


FIGURE 1. Chemical structures of hydralazine, minocycline, propylthiouracil (PTU), levamisole and cocaine. There is a paucity of information regarding structural similarities and differences of these compounds in the literature; therefore, they are represented here for visual review (created using DrugBank).

	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

- **Propylthiouracile - PTU**
  - 20~64% des patients developpent des ANCA anti-MPO
  - Titres élévés
  - Multispécifiques: anti-lactoferrin, cathepsir protein
  - c-ANCA anti-PR3 rares
  - Vascularite ches 5-10%
    - Dont ¼
    - PnI, HAD, capillarite pulmonaire

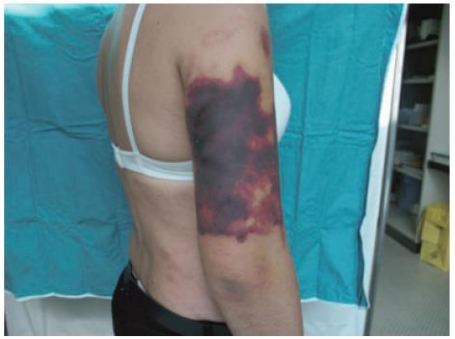


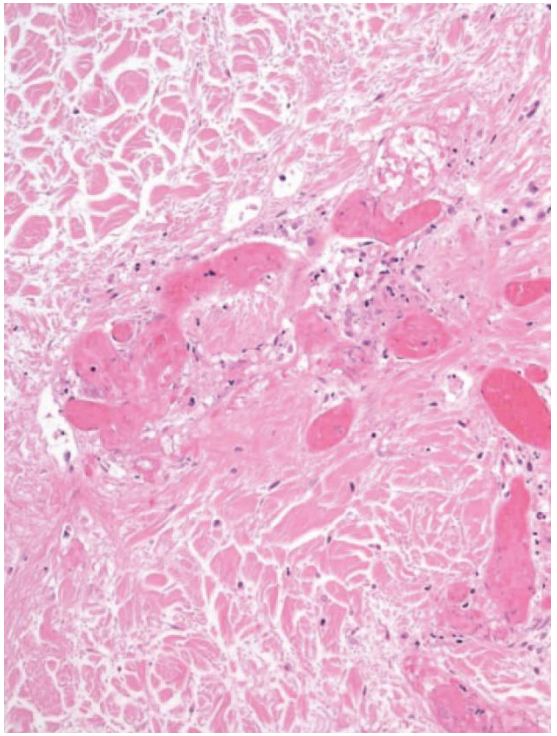
FIG. 1. Hemorrhagic skin lesions involving the upper arms (right) with rapid onset.

- **Levamisole (cocaine)**
  - 70% des saisies coupées avec lévamisole
  - 0.1-10% en masse
  - Neutropénie p-ANCA, APL+ – thrombocytopénie
  - Etat actuel: ~200 cas publiés
    - Age 18-64
    - Cocaine inhalée ou fumée
    - Lévamisole confirmé 28%
    - Neutropénies 69%
    - Complications cutanées 41%
    - Récidive à la réexposition: 55%
    - Mortalité 1.6%

- Le profil des Ac (%)
  - ANA: 21
  - ANCA: 46
  - C-ANCA 14%
    - PR3 20
  - P-ANCA 38 (1/10240)
    - MPO 27
  - ACL 16
  - Anti-HNE 13 (CIMDL)


A


B



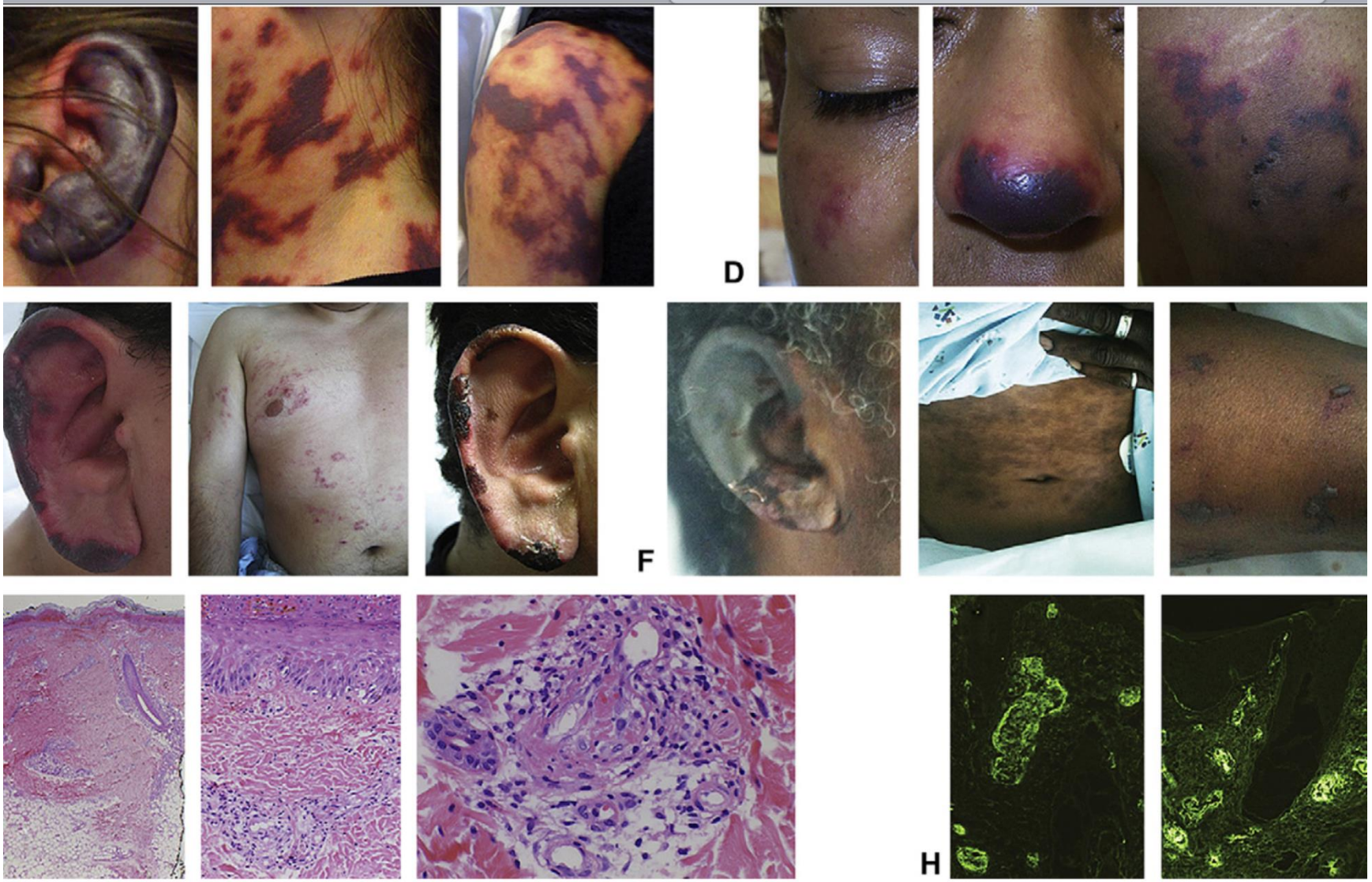
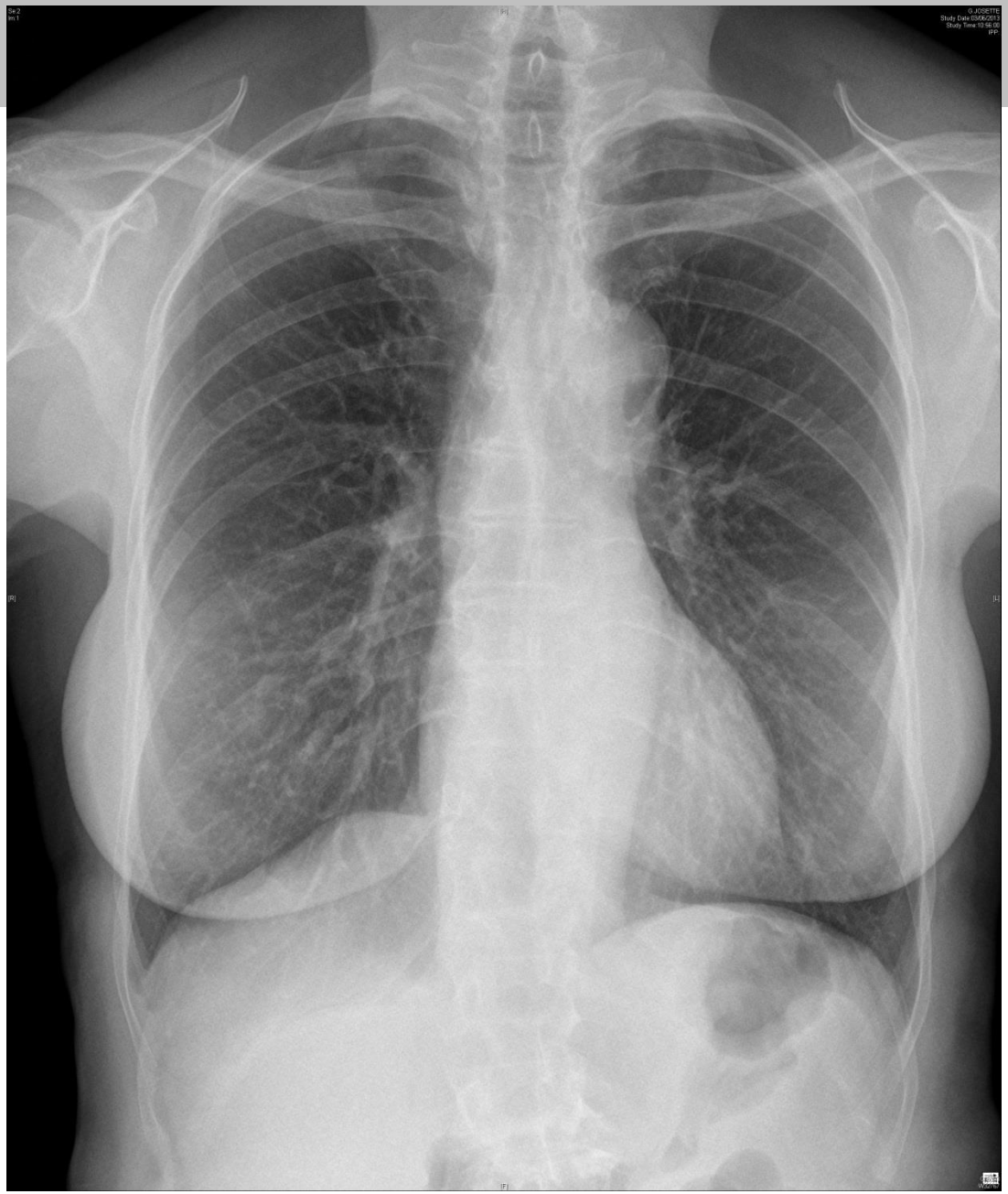
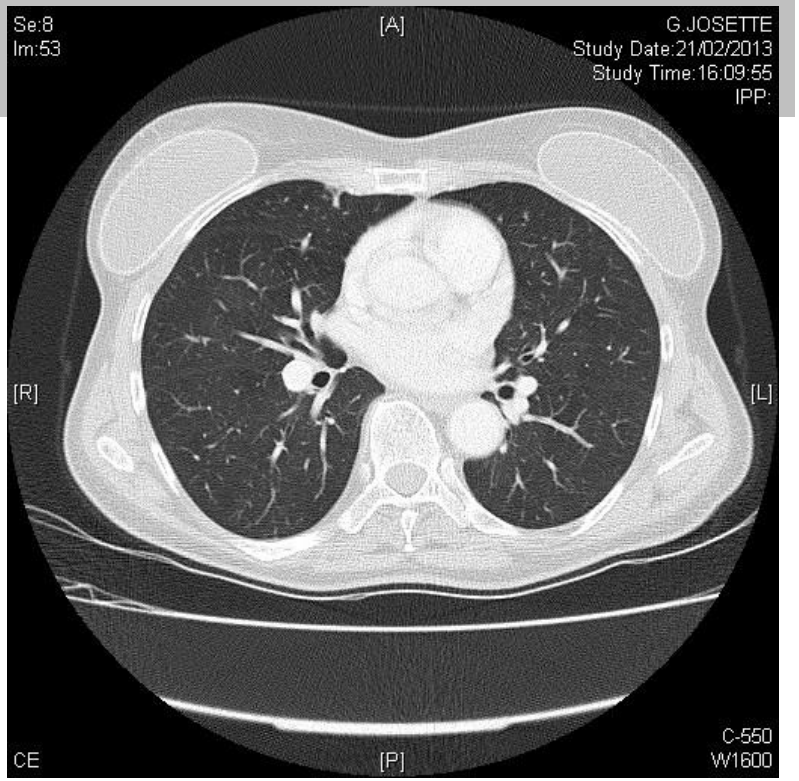


FIGURE 1. Cutaneous defects 4 and 16 days from allegedly smoking free-base co

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




Se:8
Im:53
[A]
G.JOSETTE
Study Date:21/02/2013
Study Time:16:09:55
IPP:
[R]
[L]
CE
[P]
C-550
W1600

- 32 cas
- ACL, SSA, MPO cryoglobulinémie

Immunol Res
DOI 10.1007/s12026-013-8401-3

ETIO PATHOGENESIS OF AUTOIMMUNITY

Silicone implant incompatibility syndrome (SIIS): A frequent cause of ASIA (Shoenfeld's syndrome)

J. W. Cohen Tervaert · R. M. Kappel

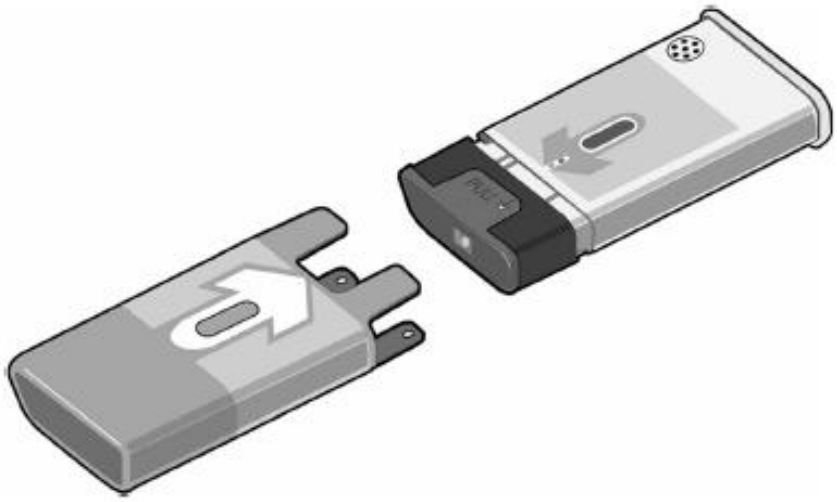
Jan Willem Cohen Tervaert

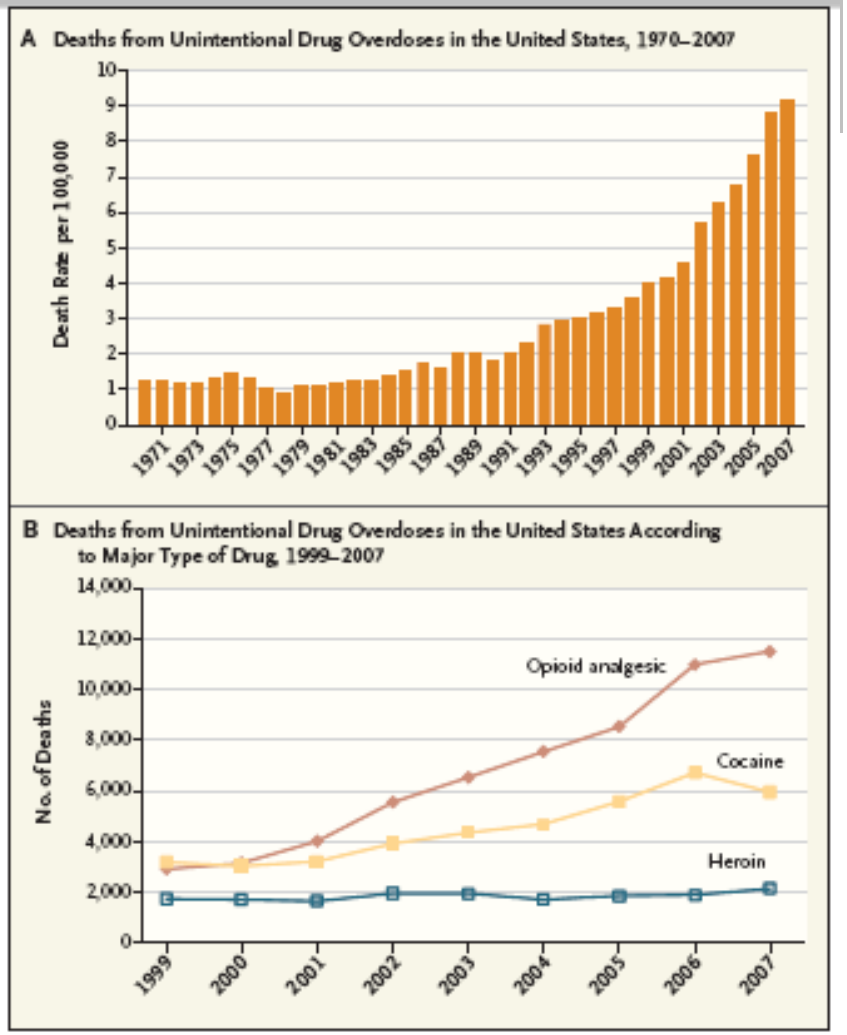
Abstract Silicon has a molecular mass of 28 daltons. In nature, silicon is found as silicon dioxide (silica) or in a variety of silicates (e.g., in talc or asbestos). Furthermore, silicon is present in silicones, polymerized siloxanes, which are often used as medical silicones in breast implants. Silicon exposure is associated with different systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, and vasculitis. Remarkably, silicon in silicone-filled breast implants is considered to be safe, not increasing the risk of developing autoimmune diseases. We analyzed the impact of silicone-filled breast implants on the immune system in 32 consecutive patients attending a specialized autoimmunity clinic. All 32 patients had silicone implant incompatibility syndrome and complaints fulfilling the diagnostic criteria of ASIA (autoimmune/inflammatory syndrome induced by adjuvants). Furthermore, in 17 of the 32 patients, a systemic autoimmune disease was diagnosed, and 15 of the 32 patients had an impaired humoral immune system. Patients developed symptoms and signs after long-term follow-up, suggesting that these symptoms and signs started after implant aging and/or rupture. We postulate that silicon in silicone-filled breast implants may increase the risk of developing (auto) immune diseases and immune deficiencies.

Keywords Silicone implants · ASIA · Adjuvants · Vasculitis · Connective tissue diseases · Immunodeficiencies

- Maladie à anti-GBM – Goodpasture
  - Lazor *et al.*, Medicine 2007: 28 cas
    - Tabac
    - Cocaine 4
    - Marijuana 3
    - Heroïne 1
    - Diesel 1
    - Insecticides 1
    - Gaz lacrymogènes 1

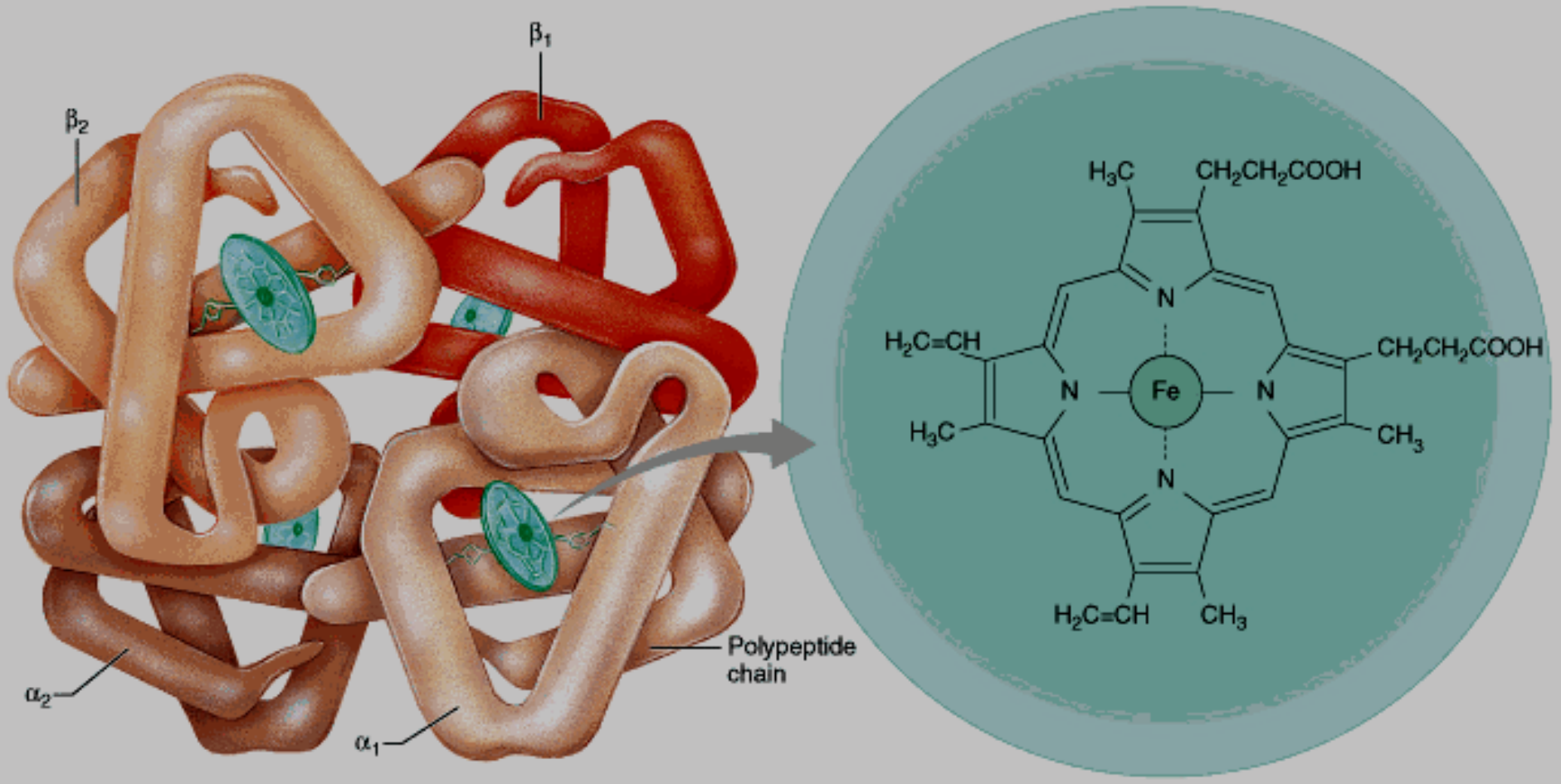
- Ventilatory depression
- Apnea – ventitlatory arrest
  - Naloxone





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

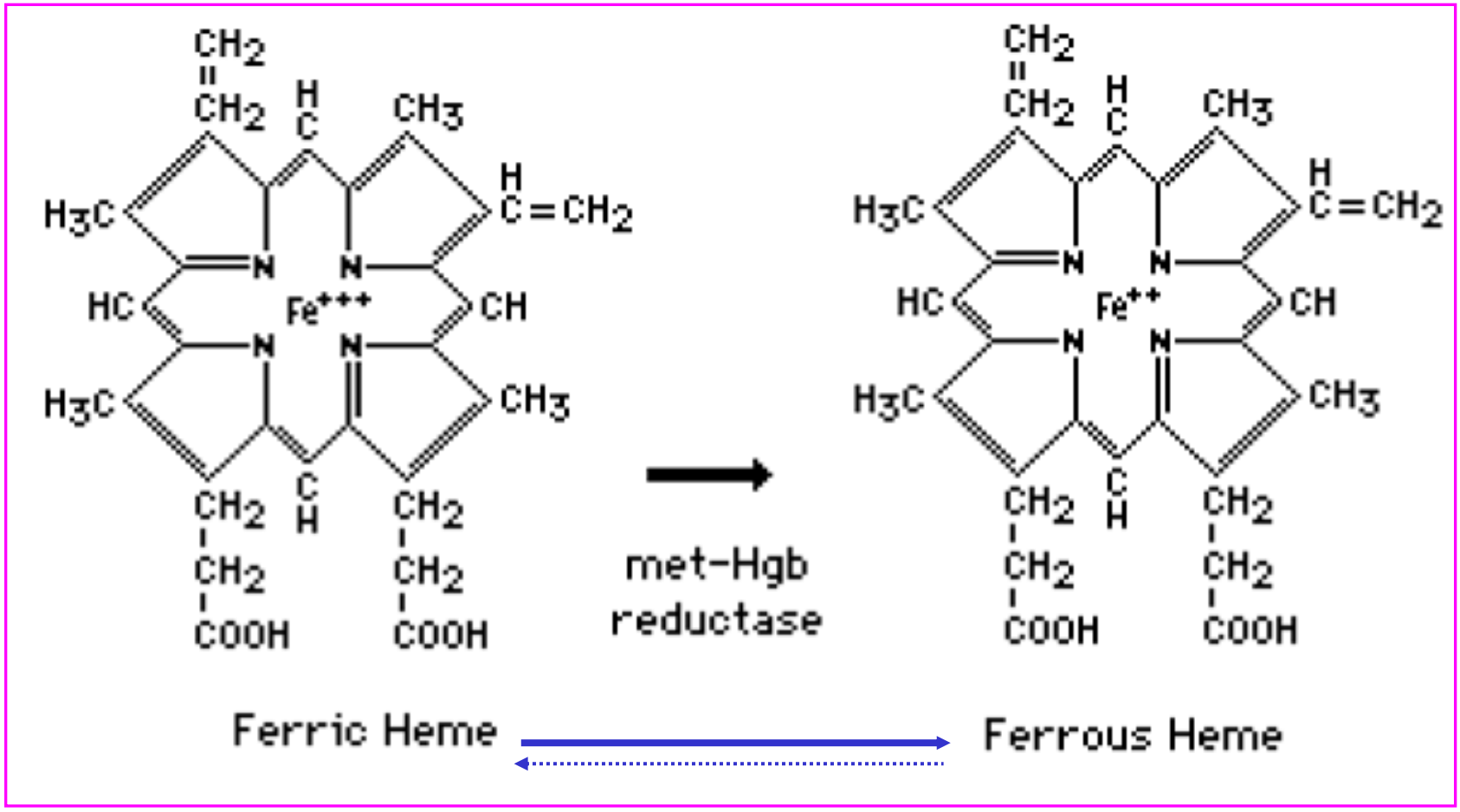
Shown are nationwide rates of death from unintentional drug overdoses from 1970 through 2007 (Panel A) and the numbers of such deaths from opioid analgesics, cocaine, and heroin from 1999 through 2007 (Panel B). Data are from the National Vital Statistics System, Centers for Disease Control and Prevention.

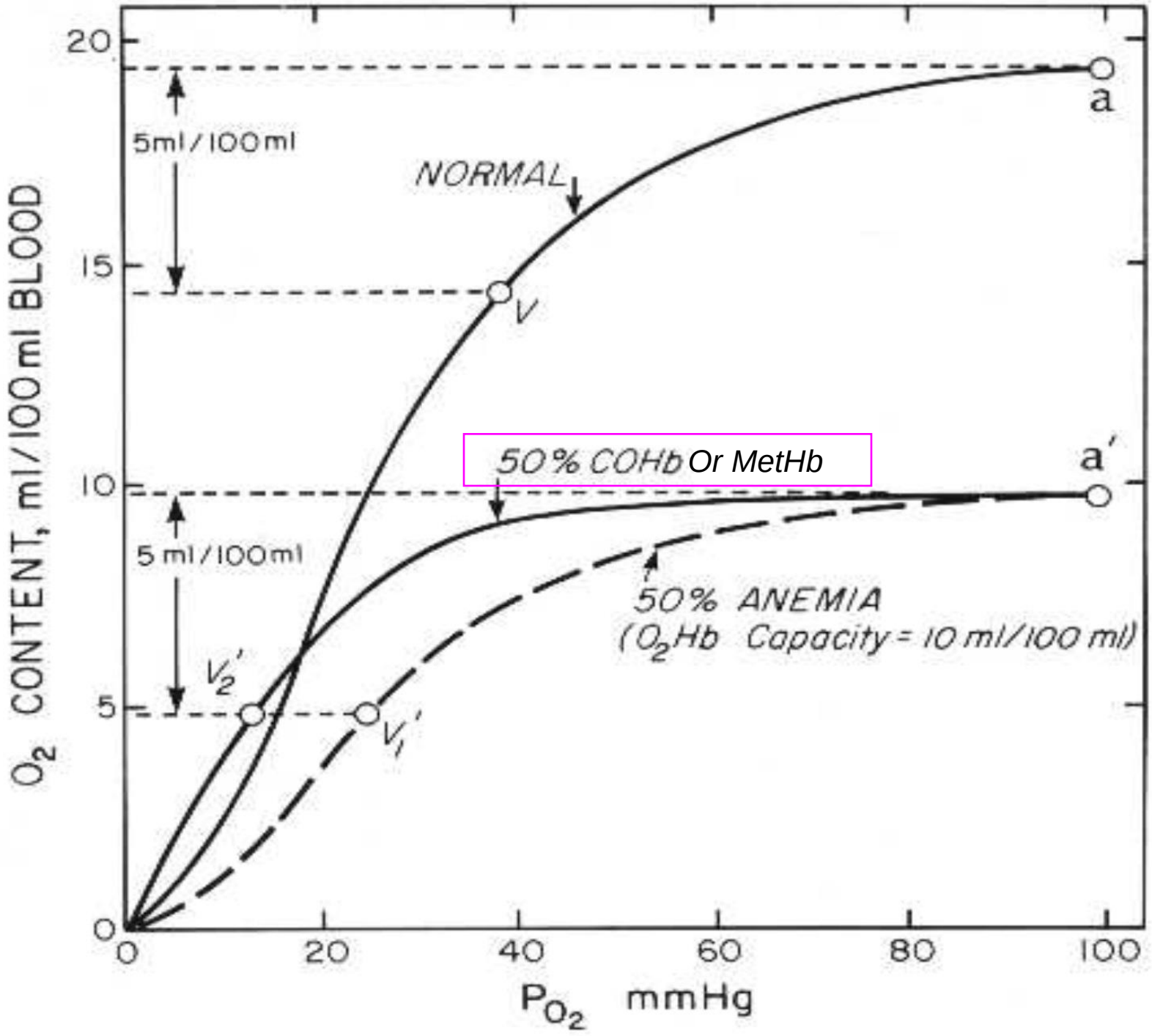


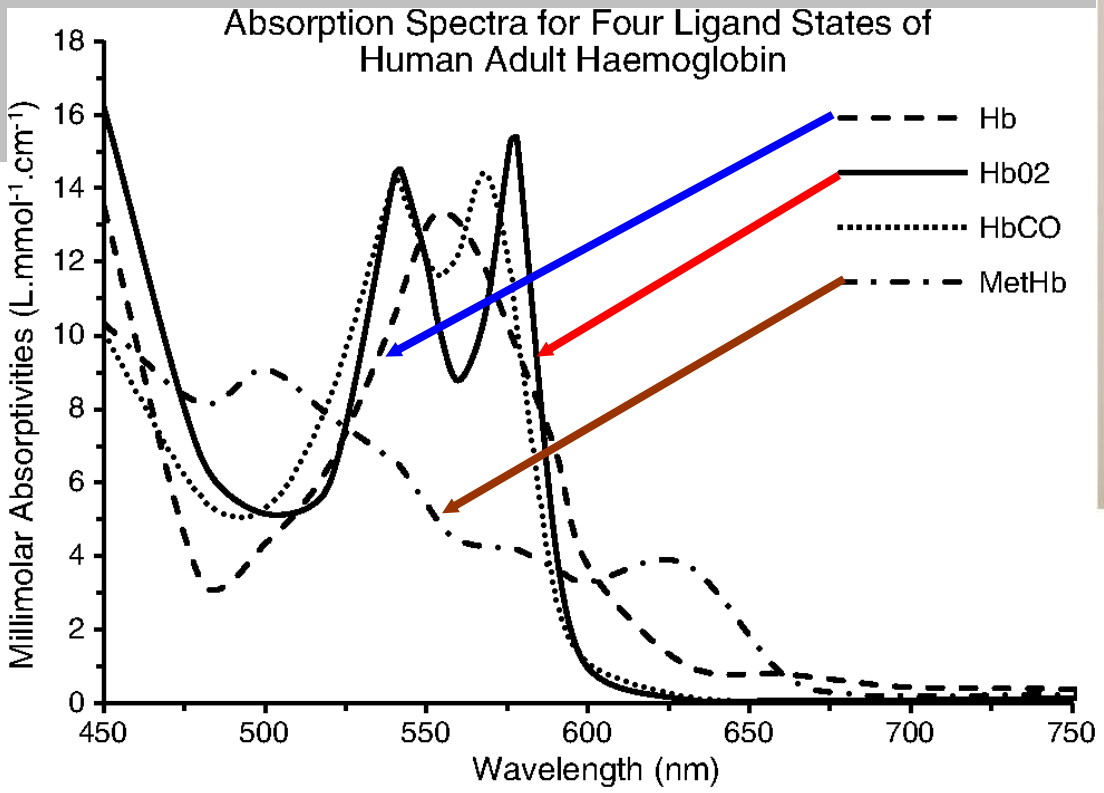
(a) Hemoglobin

(b) Iron-containing heme group

- Methemoglobin
- Full 4xFe3+ MetHb unable to carry O2




20
15
10
5
0
O2 CONTENT, ml/100 ml BLOOD
5ml/100ml
NORMAL
V
a
50% COHb Or MetHb
a'
5 ml/100ml
50% ANEMIA
(O2Hb Capacity = 10 ml/100 ml)
V2'
V1'
0
20
40
60
80
100
PO2 mmHg


Absorption Spectra for Four Ligand States of Human Adult Haemoglobin
Millimolar Absorptivities (L.mmol-1.cm-1)
Wavelength (nm)
Hb
Hb02
HbCO
MetHb
0
2
4
6
8
10
12
14
16
18
450
500
550
600
650
700
750


Pulse Oximeter
98
075


1.5
3.0
%SpMet
96
88
%SpO2
1.5
3.0
%SpMet

- Diagnosis
  - Central, blue-gray slate skin discoloration (‘cyanosis’)
  - Chocolate-brown blood
  - Blood does not turn red on paper or if bubbled with O2
  - Low or spurious (~80%) SpO2
  - PaO2 (dissolved O2) normal
  - SaO2 computed from PaO2 falsely normal
  - SaO2 minus SpO2 >5%: saturation gap
  - Cooxymetry 4-wavelength diagnostic (HbO2, deoxy, CO, MetHb)
  - Hemolytic anemia in some

- Methemoglobin
  - Normal <1%
  - Warning >2%
  - >15-20%: symptoms
  - >50-70%: risk of death
- Typical drugs
  - Benzocaine, dapsone, NO
- Management
  - Drug discontinuation
  - Oxygen therapy
  - Methylene blue - Exchange transfusion - HBO

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]

Expositions domestiques

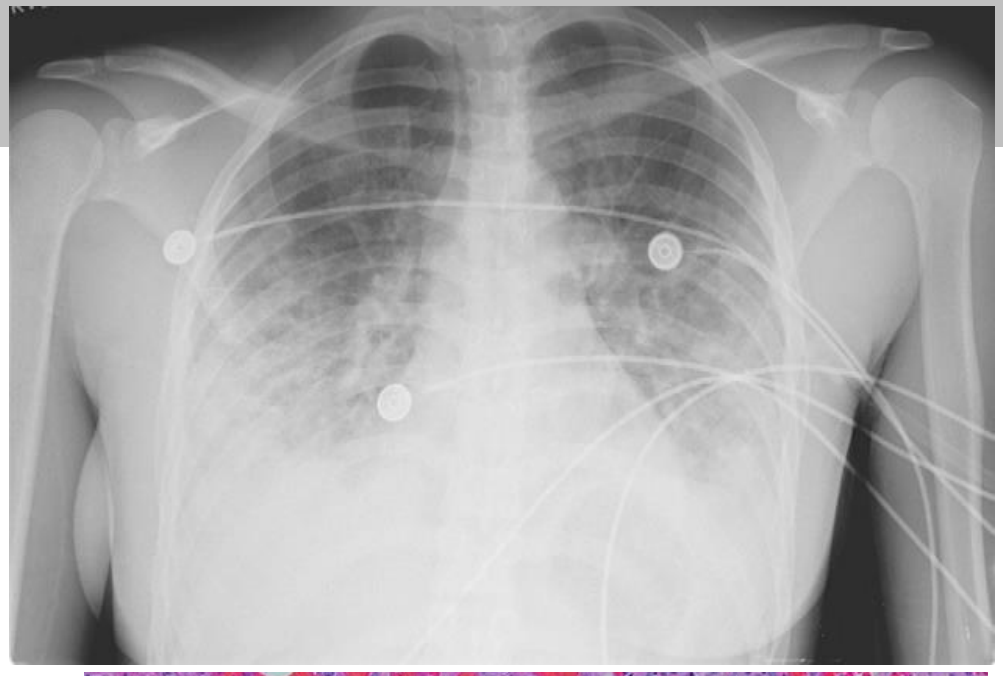
- Imperméabilisants
- Caustiques
- KMnO4
- Rachacha (morphine+codeine)

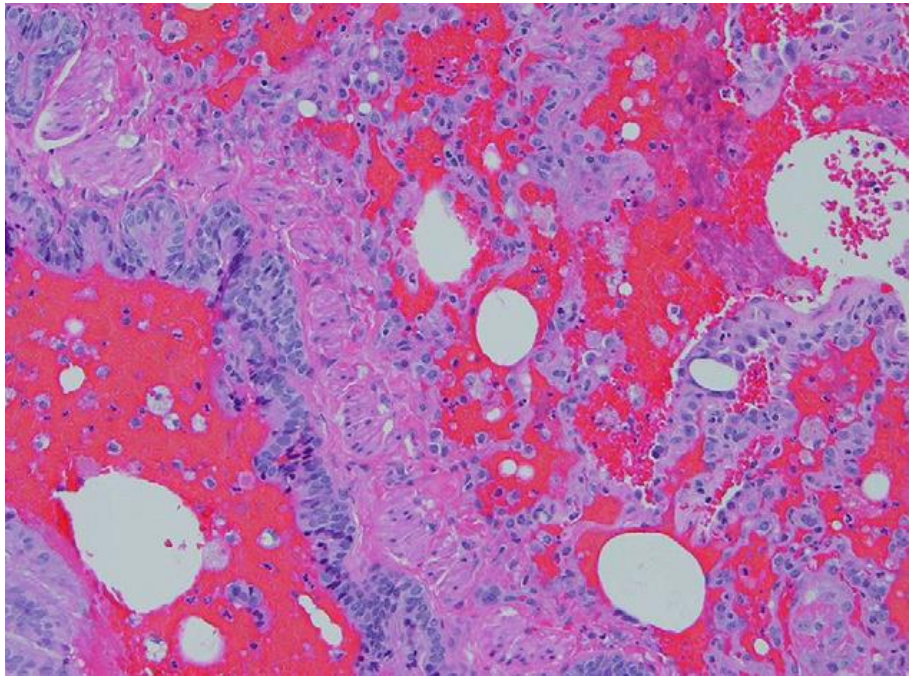
- Sutter et al.
  Fatal Fentanyl: One Pill Can Kill
  Acad Emerg Med 2016

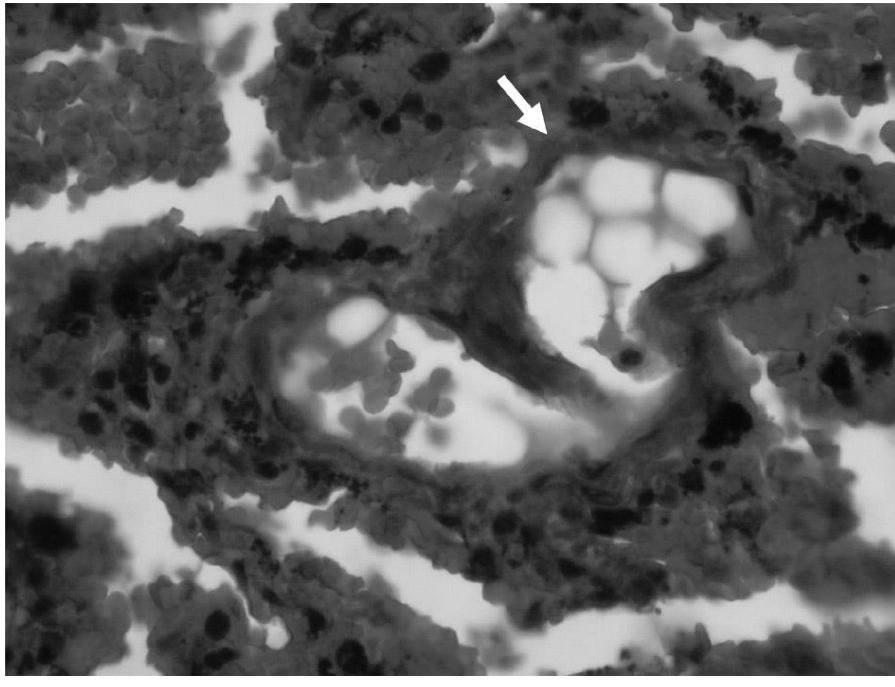

SMOKING AREA
SMARTHEADS
Powered by:
FOCUS
PLANET


HESS


Viroll's

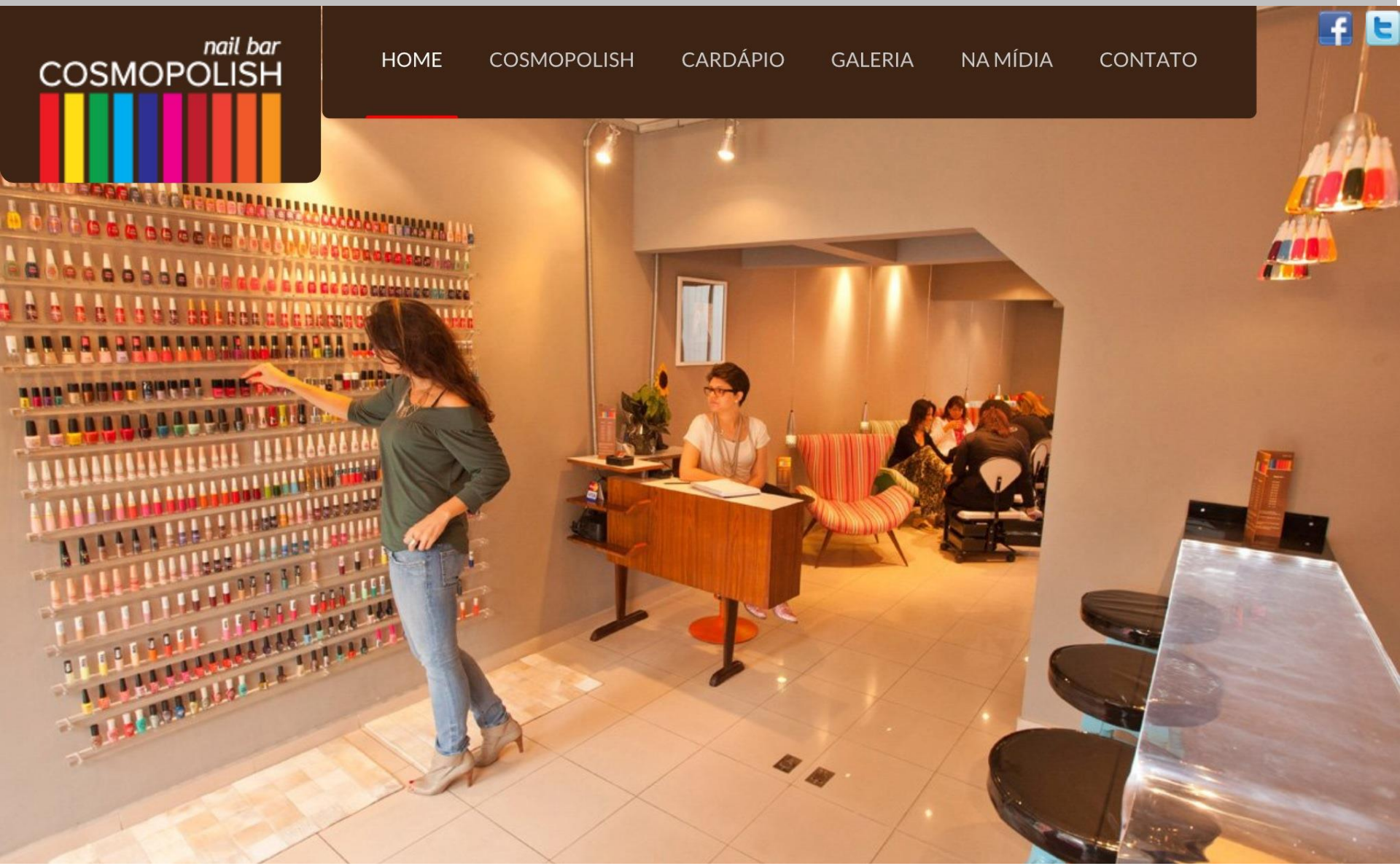


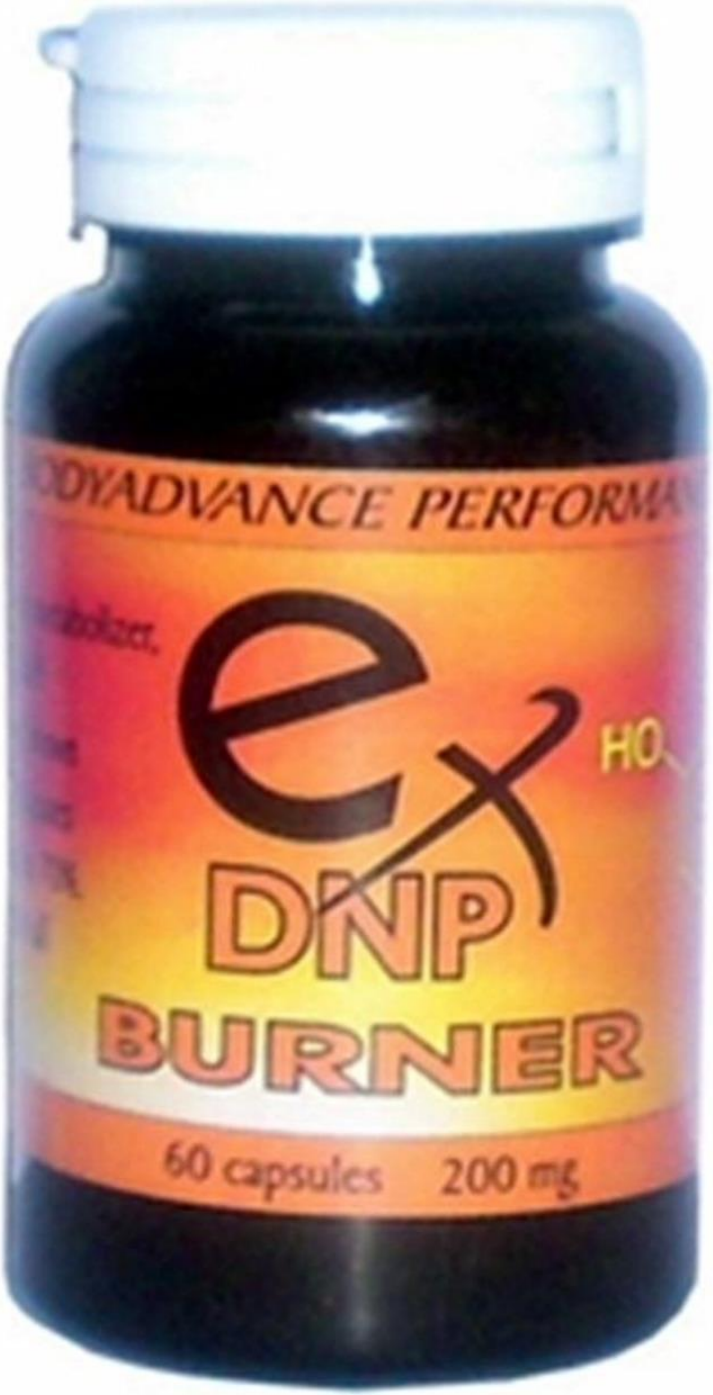




nail bar
COSMOPOLISH

HOME COSMOPOLISH CARDÁPIO GALERIA NA MÍDIA CONTATO




BODYADVANCE PERFORMA
ex
HO
DNP
BURNER
60 capsules 200 mg

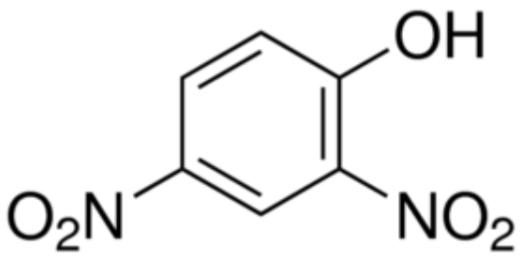
D198501 ALDRICH

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**

POPULAR DOCUMENTS: **SPECIFICATION SHEET (PDF)** | **FTNMR (PDF)**

Commander | Sécurité & Documentation | Protocoles et articles 1 | Documentation référencée 38

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

LEGAL NOTICE

POPULAR

100 x Capsules (200mg) DNP UK BUY ONLINE

£ 70.00 ~~£ 100.00~~ -30%

Add to cart

More

30 x Capsules (200mg) 2,4-Dinitrophenol...

£ 28.00 ~~£ 40.00~~ -30%

Add to cart

More

50 x Capsules (200mg) 2,4-Dinitrophenol...

£ 42.00 ~~£ 60.00~~ -30%

Add to cart

More

pictures to prove we make capsules

£ 0.00

Add to cart

More

2, 4-dinitrophenol

- Sold from the Internet
- Oxidative phosphorylation uncoupling in mitochondria
- Reliance on anaerobic Krebs cycle
- Energy deficit: adipose tissue (-> weight loss)
- Energy converted to heat
- Thermal disruption of enzymes/cells/organism
- Hyperkalemia, metabolic acidosis, renal damage
- Management: early charcoal, cooling, ?dantrolene
- Early hemoperfusion
- If it does, does improve within 6hrs

Kids & adults

- Household products
- Disinfectants
- Pharmaceuticals
- e-liquid
- Kerosene (soft drink bottles)
- Meth lab (poisoning, burns)
- Brodifacoum rodenticide
- Paraquat
- Organophosphates
- Cinnamon

Table. Selected Nonpharmaceutical Household Products That Are Toxic in Children

- Alcohols
  - Beverage ethanol
  - Methanol (windshield wiper fluid)
  - Ethylene glycol (antifreeze)
- Caustic agents
  - Alkalis (drain and oven cleaner, perm relaxers, Clinitest tablets)
  - Acids (toilet bowl cleaners, antirust compounds)
- Food-flavoring additives
  - Methylsalicylate (oil of wintergreen)
- Hydrocarbons
  - Kerosene
  - Lamp oil
  - Mineral seal oil (furniture polish)
  - Mineral spirits (paint thinner)
  - Naphtha (lighter fluid)
- Industrial chemicals
  - Methylene chloride (paint stripper)
  - Selenious acid (gun bluing)
  - Zinc chloride (soldering flux)
- Nail products
  - Acetonitrile (sculptured nail remover)
  - Methacrylic acid (artificial nail primer)
  - Nitromethane (artificial nail remover)
- Pesticides and/or insecticides
  - Organophosphates
  - Lindane
  - Paraquat

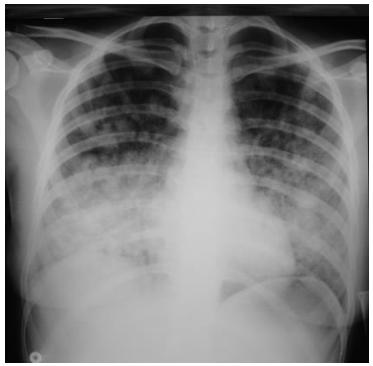
Conclusion

- Fréquence
- Diversité
- Exclusion
- Degré de certitude <-> poursuite/arrêt du M
- Influence des substances non M
- Brillant mais difficile
- Evolution pneumotox.com

Substances illicites

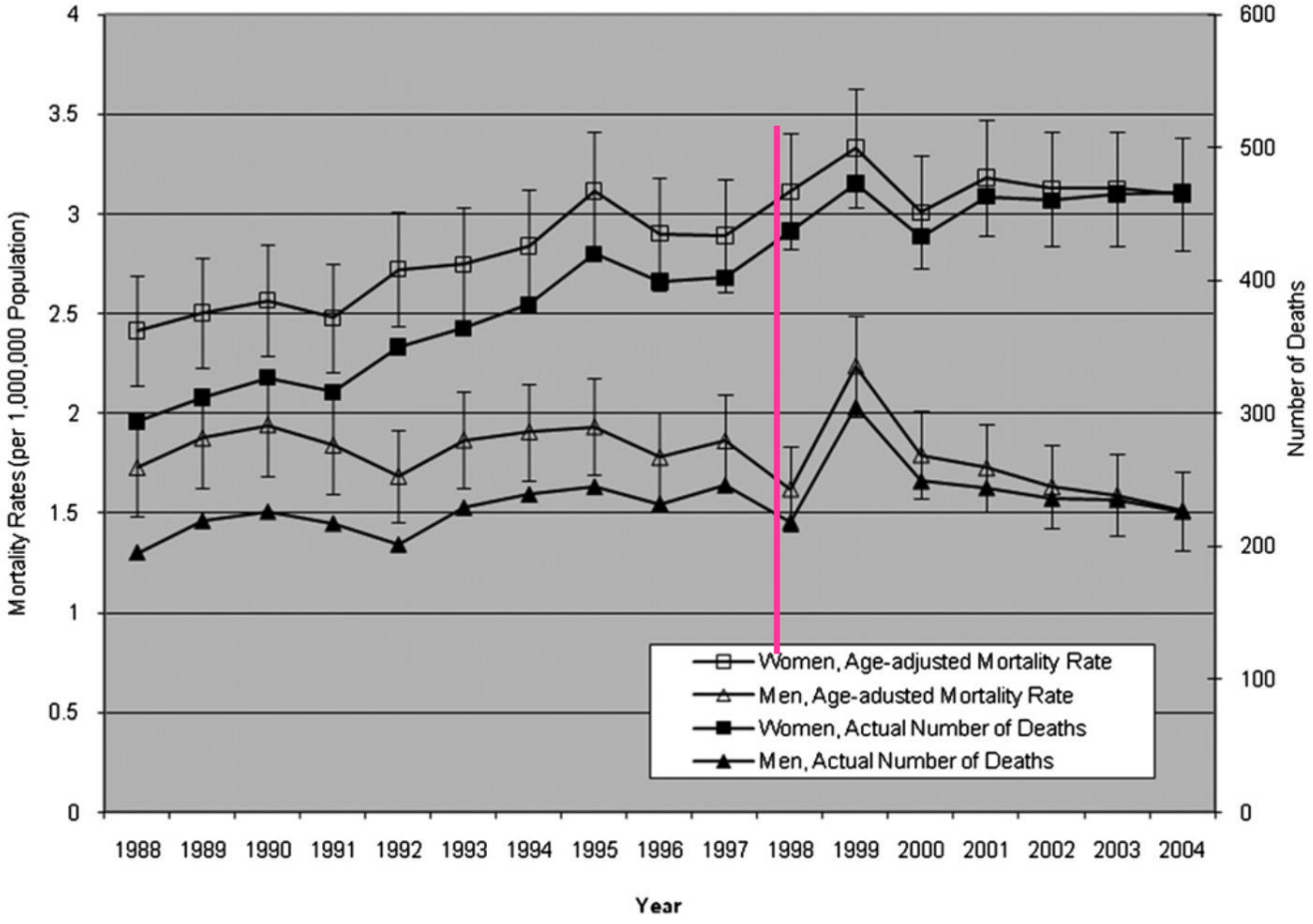
- **Cannabis, héroïne, opioïdes de synthèse, additifs, adultérants**
  - Tableaux d'urgence
    - Bronchospasme soudain grave (H)
    - HAD (C)
    - Pneumopathies aiguës à éosinophiles (C)
    - SDRA
    - Brûlures
    - PNO
    - PNM

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



Biothérapies et pathologie interstitielle ‘ILD’

- 1-De nombreux facteurs de confusion



Prévalence~10%

Figure 2. Age-adjusted mortality rates (per 1,000,000 population) and actual number of deaths per year among decedents with rheumatoid arthritis–interstitial lung disease (RA-ILD), 1988 through 2004 (*error bars*, 95% confidence intervals).

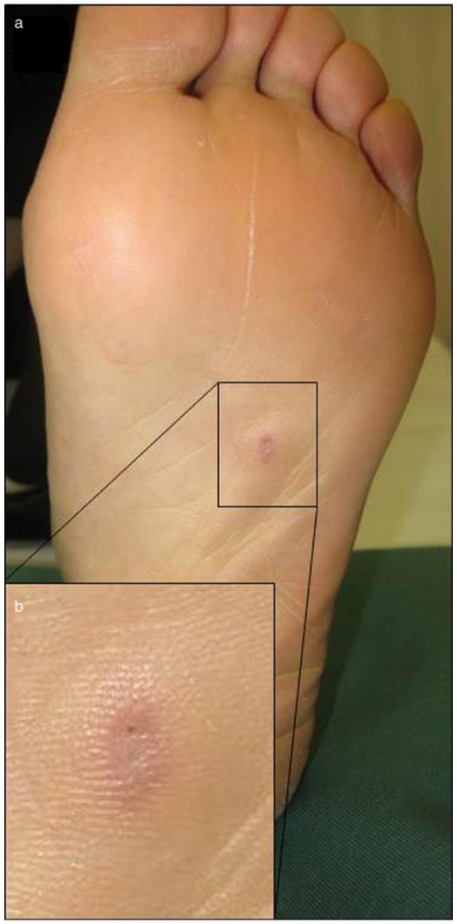
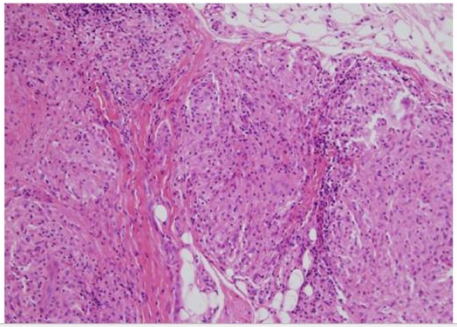


Figure 2 The patient developed a small, painful subcutaneous nodule (black circle) on the sole of her foot that was 10 mm in diameter 10 months after the initiation of therapy. The patient had no complaints about the sole of her foot before treatment.

ated giant cells (Fig. 3). Specific stains showed no evidence of bacterial, fungal or mycobacterial organisms. Biopsy findings were interpreted as consistent with sarcoidosis, although the skin lesion disappeared around the time of biopsy. Further examination was performed to evaluate systemic involvement. Laboratory studies demonstrated moderate leukocytopenia (2800/μL), elevated lysozyme (10.5 μg/mL; normal, 5.0–10.2), and normal angiotensin-converting enzyme (16.9 U/mL; normal, 8.3–21.4) and serum calcium (9.1 mEq/L). Her tuberculin skin test was negative, but ophthalmologic examination revealed uveitis. A chest X-ray (Fig. 1b) and thoracic computed tomography (CT) taken 2 months after combination therapy showed multiple bilateral, paratracheal, subcarinal and hilar adenopathies (Fig. 1d), and a diffuse micronodular interstitial pattern of the lungs (Fig. 1e). Transbronchial lung biopsy revealed the presence of multiple non-caseating granulomas with multinucleated giant cells (Fig. 4). The bronchoalveolar lavage fluid level of lymphocytes was elevated at 38.7% compared with macrophages (56.3%) and neutrocytes (5.0%) in a total cell density of $1.67 \times 10^5/mm^3$. An increased ratio of CD4/CD8 cells of 2.33 was noted. Based on these findings, the patient was diagnosed as having sarcoidosis. She was observed carefully without any additional medication because no significant systemic symptoms were noted. A chest CT taken 20 months after combination therapy showed improvement (Fig. 1f,g). She was also asymptomatic for over 3 years of follow up, and repeated hematological

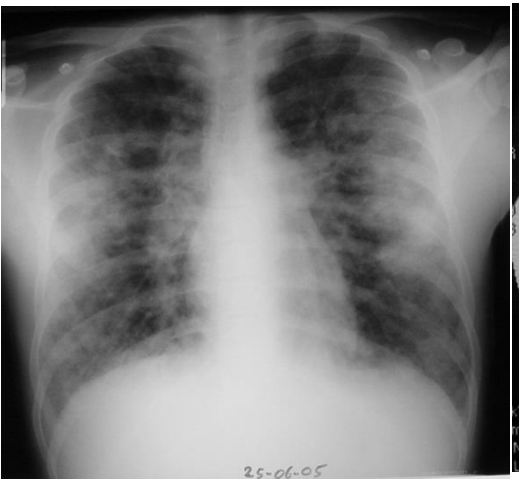


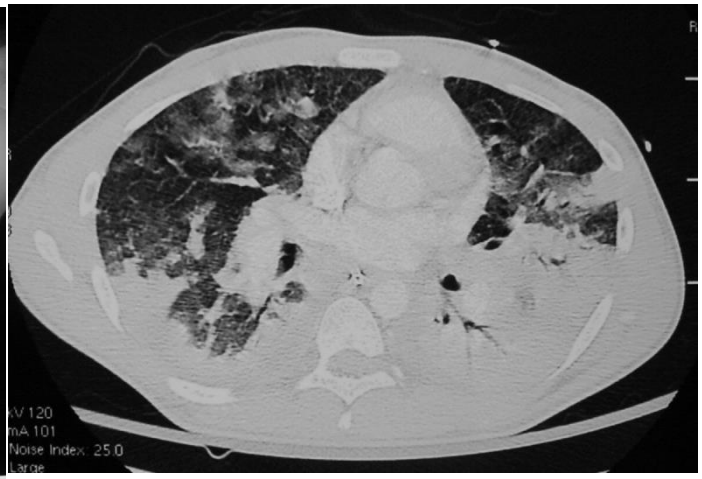
- **Maladies générales et médicaments**

DRESS

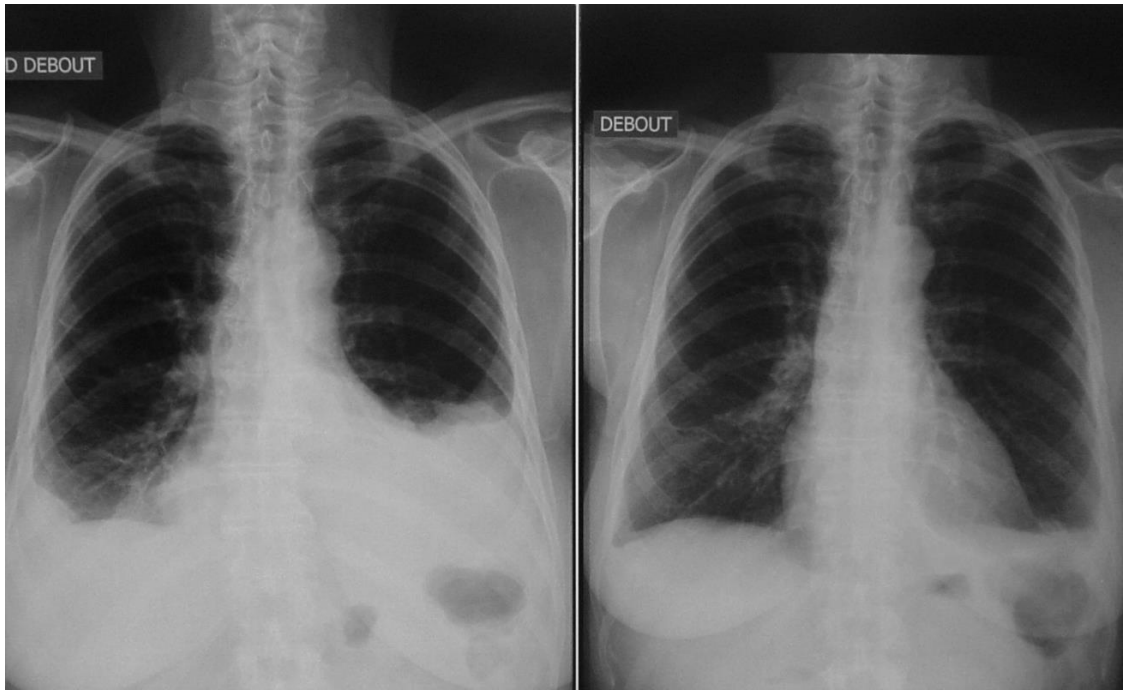
- **Um, 2010**
  - 38 patients: 18 hommes
    - Anticonvulsivants (47.4%)
    - Antibiotiques (18.4%) (minocycline)
    - AINS (13.2%)
    - Allopurinol (5.3%)
  - Latence variable: 3-105 j M 25j
  - Récupération 36 patients (94.8%)

- Rash
- Eosinophilie, cytopénie
  lympocytes atypiques
- Atteintes viscérales
  Rein, foie, SNC, TD, adénopathies
- Myocardite fulminante
- EoP *ca*. 15%





- **Lupus et biothérapies**
  - Ramos Casals 2007
  - 92 cas
  - Infliximab 44%, etanercept 40%, adalimuab 16%
  - ANA 79%
  - Antids-DNA 72%
  - Polysérite 9 (12%)



Sd de Churg-Strauss - EGPA

- **Arguments qui pourraient disculper les anti-LT**
  - Escalade ttt
    - Introduction des anti-LT: asthme plus sévère
  - Démasquage
    - Anti-LT -> réduction / arrêt des corticoïdes
  - Abstinence des corticoïdes
- **Arguments en faveur d'un lien de causalité**
  - Chronologie suggestive
  - Survenue au cours d'asthmes modérés
  - Survenue au cours d'asthmes dont la corticothérapie est restée inchangée
  - SCS survenu sous anti-LT, et récidivant après sa réintrodution
  - SCS idiopathique subissant une poussée après introduction *de novo* d'un anti-LT

- Médicaments chez l’atopique
- Injecton par personnel seul
- Retard diagnostique
- Interactions, dosage
- Recommandations non appliquées
- Bilans de départ et périodiques non régulièrement effectués
- Biopsies superflues
- Pathologiste non informé des médicaments

- Chang J Autoimmun 2009

Drug	Approximate date of first report	Incidence/cases reported	Diseases/symptom complexes	Clinical features	Autoantibodies reported	Dose dependent
Procainamide	1962	Approx 20%	DIL	Arthritis, arthralgias, fever	ANA, anti-histone antibodies, anti-histone–DNA complex antibodies	Yes
Minocycline	1992	>60 cases	DIL, autoimmune hepatitis, autoimmune thyroiditis	Rash, arthralgias, arthritis, elevated liver enzymes, jaundice	ANA Anti-ds-DNA pANCA	No
Hydralazine	1968	50% autoantibodies, 5–10% autoimmune disease	DIL, vasculitis	Fever, rash, arthralgias, cutaneous involvement, vasculitis, mylagias, pleuritis, leukopenia	ANA, anti ds-DNA, ANCA	Yes
Sulfasalazine	1977	Case reports	DIL, vasculitis	Inflammatory arthropathy, cutaneous vasculitis	Anti-(H2A-H2B)DNA, anti ds-DNA	No
Aromatase inhibitors [101]	1998	3.5%–27.8%	DIL, sicca syndrome, Sjogren's syndrome, inflammatory arthropathies	Arthralgias	Not reported	No data
Isoniazid	1968	Approx 22%	DIL	Arthralgias, arthritis, anemia, fever, pruritis	Anti-(H2A-H2B)DNA	No
Statins	2001	28 cases	DIL, dermatomyositis, polymyositis, lichen planus pemphigoides	Myalgias, polyarthralgias, polyarthritis, leukopenia, photosensitivity, serositis	ANA, Anti Jo-1, Anti-histone, Andi-dsDNA	No
Cyclosporin	1988	N/A	GVH disease – in rat only, scleroderma – like disease	N/A	N/A	No
Quinidine	1988	7 cases	DIL	Polyarthropathies	ANA, anti-histone antibodies	No
Methyldopa	1968	0.02%	Autoimmune hemolytic anemia	Hemolytic anemia	+ Coombs test	No data

- p-ANCA positifs dans
  - 50% des lupus sous PTU
  - 67-100% des lupus sous minocycline
  - MPO

- **Yu, 2007: vascularite avec atteinte rénale sous PTU (43.0 ± 31.2 mois) Yu, 2007**
  - 15 patients (13F) hématurie (100%), protéinurie (100%), IR (47%)
  - Atteinte pulmonaire: 5/15 (prévalence similaire aux vascularites ANCA+ primitives)
  - p-ANCA 15
  - Spécificité
    - Myeloperoxidase 15
    - Cathepsin G 9
    - Elastase 8
    - Lactoferrin 7
    - Azurocidin 5
    - PR3 4

Statines et sd. dysimmunitaires

- Noël. JEAD 2007; 21: 17
  - Lupus 10
  - Lupus cutané 3
  - DM 7
  - PM 7
  - Lichen plan 1
  - Hépatite 2
  - Délai moyen 12.8 ± 18 mo
  - Corticoïdes et/ou IS 25/28
  - Mortalité 2 (SDRA)

- **APL**
  - Asherson 1998
  - Thiazide, capropril, contraceptive
- **Sweet**
  - GM-CSF

- **Conclusion**
  - Palette des atteintes, certaines gravissimes
  - Eviction précoce du médicament
  - Preuves de causalité hétérogènes
  - Nécessité absolue d’écarter une infection
  - Médicaments et drogues -> déclencher
    - Anomalies biologiques d’autoimmunité
    - Avec expression pulmonaire ou systémique
    - ? Maladies de système

www.pneumotox.com/drug/index/

Rechercher

ongue involvement | Three cases with different presentation of fe..... | Pneumotox » Drug » Drug

Available on the App Store

BROWSE NEWS ABOUT CONTACT RSS

PNEUMOTOX ON LINE

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.b V.d VIII.a VIII.q IX.e X.d XVIII.l — 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

Acetazolamide — 1

SEARCH

Search by keyword

Advanced search

NOTE LEGEND ?

LEGEND PATTERNS ?

LATEST NEWS

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

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

Wed, 20 Feb 2013 16:42:42
Language

Mon, 18 Feb 2013 14:17:43

Nicardipine II.a	1
Nicergoline V.c	1
Nifedipine II.a XI.b	1
Niflumic acid I.c	1
Nilotinib V.a X.r	1
Nilutamide I.a I.b I.c I.d XV.a XV.k	3
Nimesulide I.c II.a IV.a IV.c	1
Niridazol I.c II.a IV.a	1
Nitrates XIV.a	2

Nicergoline — V.c — 1

Nifedipine — II.a, XI.b — 1

Niflumic acid — I.c — 1

Nilotinib — V.a, X.r — 1

Nilut — I.a — 3

V - Pleural and/or pericardial involvement
V.a - Pleural effusion

Nimesulide — I.c, II.a, IV.a, IV.c — 1

Niflumic acid — I.c — 1

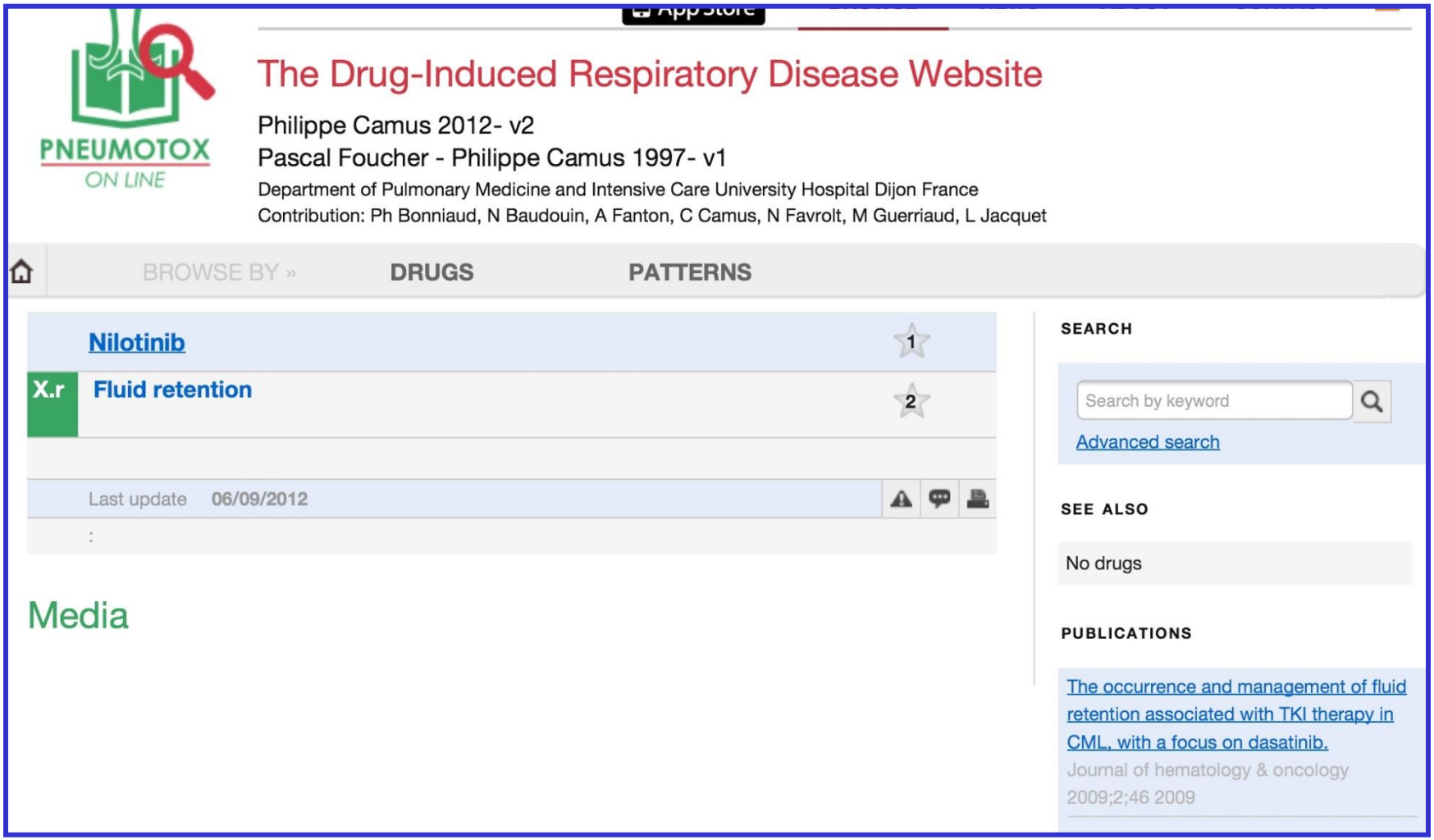
Nilotinib — V.a, X.r — 1

Nilutamide — I.a, I.b — 3

X - Systemic reactions or conditions
X.r - Fluid retention

Nimesulide — I.c, II.a, IV.a, IV.c — 1

Niridazol — I.c, II.a, IV.a — 1


PNEUMOTOX
ON LINE
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
Nilotinib
1
X.r
Fluid retention
2
Last update 06/09/2012
:
Media
SEARCH
Search by keyword
Advanced search
SEE ALSO
No drugs
PUBLICATIONS
The occurrence and management of fluid retention associated with TKI therapy in CML, with a focus on dasatinib.
Journal of hematology & oncology
2009;2;46 2009

J Hematol Oncol. 2009 Nov 12;2:46. doi: 10.1186/1756-8722-2-46.

The occurrence and management of fluid retention associated with TKI therapy in CML, with a focus on dasatinib.

Masiello D, Gorospe G 3rd, Yang AS.

Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases, University of Southern California Medical Center, 1441 Eastlake Ave Suite 7317, Los Angeles, CA 90033, USA. masiello@usc.edu

Abstract

Tyrosine kinase inhibitors (TKIs) like dasatinib and nilotinib are indicated as second-line treatment for chronic myeloid leukemia resistant or intolerant to the current first-line TKI imatinib. These are agents are well tolerated, but potent and as such should be monitored for potentially serious side-effects like fluid retention and pleural effusions. Here we present key clinical trial data and safety considerations for all FDA approved TKIs in context for effective management of fluid retention and pleural effusions. Altering the dasatinib regimen from 70 mg twice daily to 100 mg daily reduces the risk of pleural effusion for patients taking dasatinib. Should pleural effusion develop, dasatinib should be interrupted until the condition resolves. Patients with a history of pleural effusion risk factors should be monitored closely while taking dasatinib. Patients receiving imatinib and nilotinib are not without risk of fluid retention. All patients should also be educated to recognize and report key symptoms of fluid retention or pleural effusion. Pleural effusions are generally managed by dose interruption/reduction and other supportive measures in patients with chronic myeloid leukemia receiving dasatinib therapy.

PMID: 19909541 [PubMed - indexed for MEDLINE] PMCID: PMC2785832 Free PMC Article

Journal of Hematology & Oncology

BioMed Central

Review

Open Access

The occurrence and management of fluid retention associated with TKI therapy in CML, with a focus on dasatinib

David Masiello, Gerry Gorospe III and Allen S Yang*

Address: Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases, University of Southern California Medical Center, 1441 Eastlake Ave Suite 7317, Los Angeles, CA 90033, USA

Email: David Masiello - masiello@usc.edu; Gerry Gorospe - gorospe@usc.edu; Allen S Yang* - allenyan@usc.edu

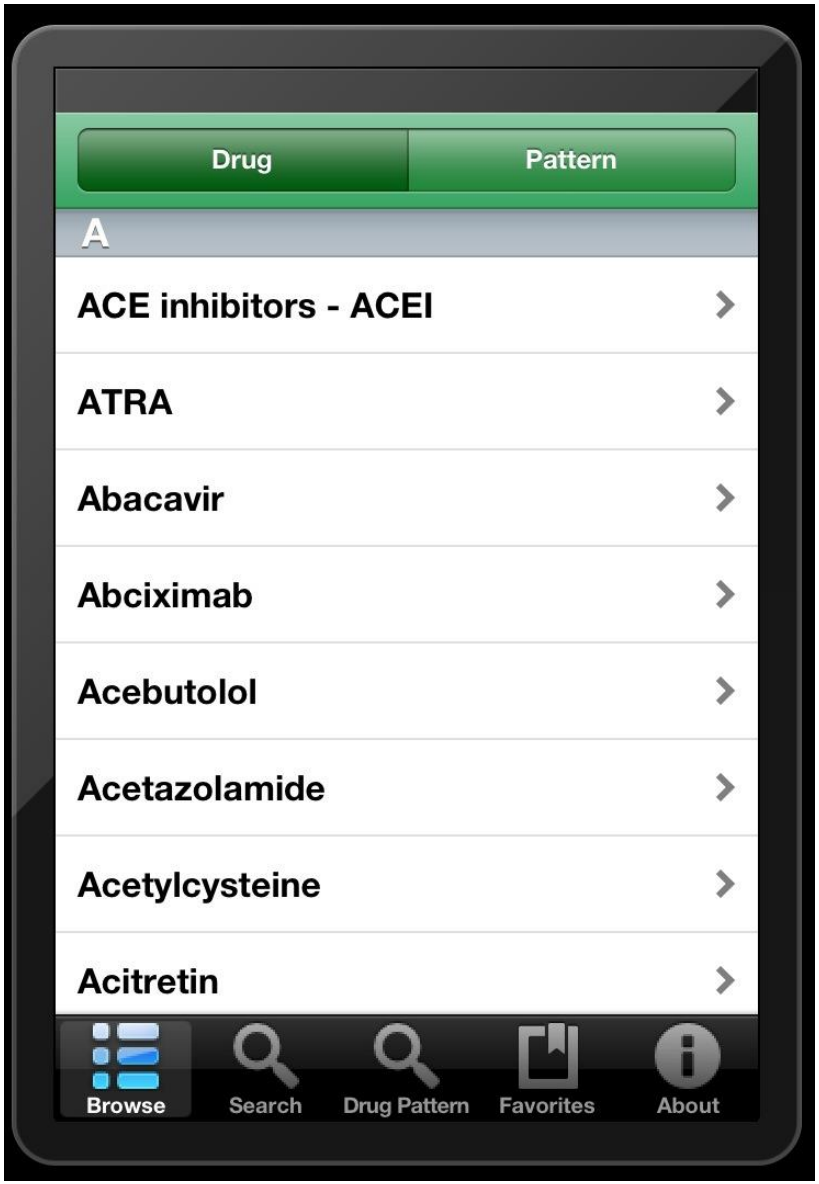
* Corresponding author

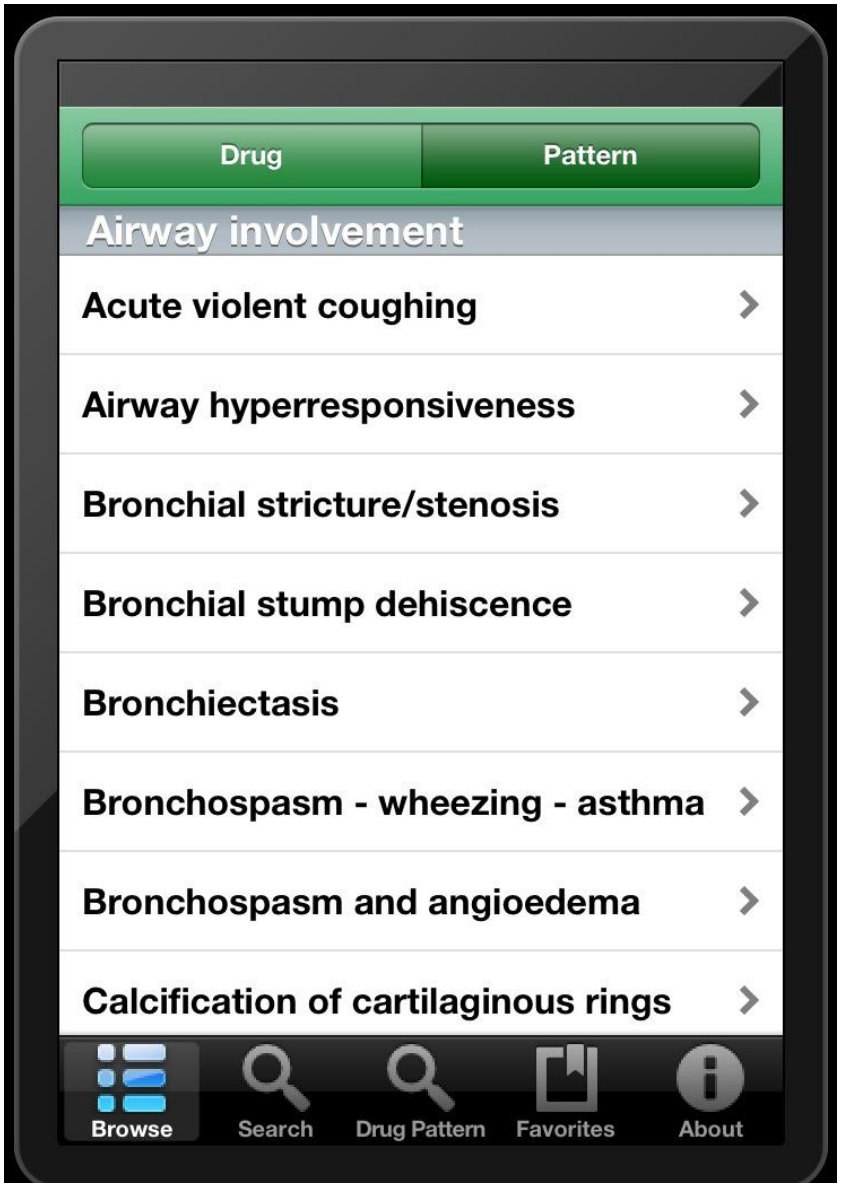
Published: 12 November 2009

Journal of Hematology & Oncology 2009, **2**:46 doi:10.1186/1756-8722-2-46

Received: 28 August 2009
Accepted: 12 November 2009

This article is available from: http://www.jhoonline.org/content/2/1/46


Drug
Pattern
A
ACE inhibitors - ACEI
ATRA
Abacavir
Abciximab
Acebutolol
Acetazolamide
Acetylcysteine
Acitretin
Browse
Search
Drug Pattern
Favorites
About


Drug
Pattern
Airway involvement
Acute violent coughing
Airway hyperresponsiveness
Bronchial stricture/stenosis
Bronchial stump dehiscence
Bronchiectasis
Bronchospasm - wheezing - asthma
Bronchospasm and angioedema
Calcification of cartilaginous rings
Browse
Search
Drug Pattern
Favorites
About

- **Comme au judo, la clé c’est la prise**