Thematic Review Series

Respiration

Respiration 2004;71:301–326
DOI: 10.1159/000079633

Interstitial Lung Disease Induced by Drugs and Radiation

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Key Words
Interstitial lung disease · Drugs · Lung damage · Lung toxicity

Abstract
An ever-increasing number of drugs can reproduce variegated patterns of naturally occurring interstitial lung disease (ILD), including most forms of interstitial pneumonias, alveolar involvement and, rarely, vasculitis. Drugs in one therapeutic class may collectively produce the same pattern of involvement. A few drugs can produce more than one pattern of ILD. The diagnosis of drug-induced ILD (DI-ILD) essentially rests on the temporal association between exposure to the drug and the development of pulmonary infiltrates. The histopathological features of DI-ILD are generally consistent, rather than suggestive or specific to the drug etiology. Thus, the diagnosis of DI-ILD is mainly made by the meticulous exclusion of all other possible causes. Drug dechallenge produces measurable improvement in symptoms and imaging in the majority of patients, whereas corticosteroid therapy is indicated if symptoms are present or drug dechallenge is without an effect. Rechallenge is justified in a minority of patients, and is discouraged for diagnostic purposes only. Pneumotox® (www.pneumotox.com) provides updated information on drug-induced respiratory disease.

Previous articles in this series: 1. Zompatori M, Bnà C, Poletti V, Spaggiari E, Ormitti F, Calabrò E, Tognini G, Sverzellati N: Diagnostic imaging of diffuse infiltrative disease of the lung. *Respiration* 2004;71:4–19. 2. Poletti V, Chilosi M, Olivieri D: Diagnostic invasive procedures in diffuse infiltrative lung diseases. *Respiration* 2004;71:107–119. 3. Chetta A, Marangio E, Olivieri D: Pulmonary function testing in interstitial lung diseases. *Respiration* 2004;71:209–213.

Introduction

Many established drugs and novel therapeutics [e.g. chemotherapeutic drugs, colony-stimulating factors, interferons, anti-tumor necrosis factor (TNF)-α and monoclonal antibodies] can produce injury of the lungs, airways, pleura and pulmonary circulation [1–6]. In addition to prescription drugs, over-the-counter medicines, illicit drugs [7], herbs [8], dietary compounds and irradiation [9] can also produce interstitial lung disease (ILD). ILD is the most common form of drug-induced respiratory disease, and this requires the same diagnostic approach as in ILD of other causes [10, 11]. A current list of drugs which can cause ILD is available (table 2) [1].

Drugs generally produce involvement of the lung in isolation. Less often, involvement of the liver is present concomitantly with involvement of the lung, or the drug produces a generalized systemic autoimmune or hypersensitivity reaction, which also involves the lung diffusely [12].

ILD corresponds to several histopathologic patterns, including true interstitial pneumonias, alveolar involvement and pulmonary vasculitis. These three patterns

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occasion pulmonary infiltrates, and since not many patients with drug-induced ILD (DI-ILD) undergo a confirmatory lung biopsy, it is often difficult to infer the histopathologic background of drug-induced pulmonary infiltrates from their appearance on imaging [11, 13]. Bronchoalveolar lavage (BAL) may also not make it possible to distinguish ILD due to drugs versus other noniatrogenic causes [14].

Drugs can produce virtually all histopathologic patterns of interstitial pneumonia, including cellular and fibrotic nonspecific interstitial pneumonia, pulmonary infiltrates and eosinophilia (PIE), organizing pneumonia (OP), lymphocytic interstitial pneumonia, desquamative interstitial pneumonia (a condition in which both the interstitium and the alveolar space are involved), a pulmonary granulomatosis-like reaction and a usual interstitial pneumonia-like pattern [15]. Respiratory bronchiolitis-interstitial lung disease, alveolar microlithiasis, Langerhans cell granulomatosis, amyloid deposits and centrilobular fibrosis have *not* been associated with exposure to drugs. Drug-induced alveolar changes include pulmonary edema, alveolar hemorrhage with or without demonstrable capillaritis, desquamative interstitial pneumonia, diffuse alveolar damage (DAD), a mimic of lipid storage disease, and an alveolar proteinosis-like reaction [15]. A few drugs cause pulmonary vasculitis [15]. A limited number of drugs (e.g. amiodarone, paraffin) produce a characteristic histopathologic pattern of involvement, which enables almost instant recognition of the drug etiology [15].

Some drugs can produce more than one pattern of histopathological involvement in the same patient. For instance, OP and eosinophilic pneumonia can coexist on the same specimen, as may DAD with pulmonary edema and/or alveolar hemorrhage. This may create confusion about which pattern dominates in one patient, unless a lung specimen of significant size is available for review [15]. For that reason, an open video-assisted lung biopsy is preferred to the transbronchial approach. A few drugs (e.g. amiodarone, bleomycin) can produce a constellation of clinicopathologic patterns of involvement.

The diagnosis of drug-induced lung disorders rests on the notion of a definite temporal association between exposure to the agent and the development of respiratory signs and symptoms (table 1) [12]. The chronological association can be evidenced at history taking, when chest radiographs taken prior to treatment with the drug are reviewed, or because drug withdrawal is quickly followed by clinical and radiological improvement. Difficulties arise when signs and symptoms develop *after* the drug is discontinued, instead of during treatment (e.g. late chemotherapy or amiodarone lung), or when drug withdrawal does not translate into improvement, as in drug-induced acute/hyperacute cellular pneumonia and pulmonary fibrosis.

Although DI-ILD accounts for only 3% of all causes of ILD [16], DI-ILD is important because drug withdrawal often results in improvement of the condition. This article is clinically oriented, and reviews drugs which cause ILD and the resulting acute and subacute or chronic patterns of involvement.

Table 1. Diagnostic criteria for drug-induced infiltrative lung disease (a high index of suspicion is needed at all times)

1	*Correct identification of the drug* This requires history taking of current and remote exposure to prescription drugs, over-the-counter medications, dietary compounds and herbs, homemade products, illicit and odd substances and radiation therapy.
2	*Singularity of the drug* In patients exposed to several drugs, the respective likelihood is evaluated against the incidence rate of pulmonary adverse effects and pattern of lung response for each drug (see Pneumotox [1]).
3	*Temporal eligibility* Time to onset of the ILD is variable. Onset of symptoms must be temporally associated with drug administration. There should be no evidence of ILD prior to treatment with the suspected drug. Thus, review of earlier chest films is required. Ideally, all signs and symptoms related to the ILD should clear after discontinuance of the specific drug. This is not the case in patients with pulmonary fibrosis. Where possible, corticosteroid therapy should not be given to selectively evaluate the effect of drug dechallenge. Recurrence with rechallenge is central to the diagnosis of drug-induced ILD. This carries intrinsic risks, as pulmonary reactions of increased severity and death may ensue. Patients who demonstrate mild ILD may be rechallenged after informed consent, only if no alternate therapy drug is available to treat the basic disease.
4	*Characteristic clinical, imaging, BAL and pathologic patterns of the reaction to the specific drug* For details, see text and Pneumotox [1].
5	*Exclusion of other causes for the ILD* Careful workup for an infection, pulmonary edema or pulmonary involvement from the background condition is required.

Drugs Causing ILD

The epidemiology of DI-ILD has changed with time. For example, OP associated with the use of the early antihypertensive drugs hexamethonium and mecamylamine disappeared in the early 1960s [1]. The prevalence of

nitrofurantoin lung decreased from a high in the 1960s to a low in the 1980s. However, this condition is on the increase again, as the drug regains popularity as a urinary antiseptic. Amiodarone pulmonary toxicity (APT) was recognized in 1980, and remains a significant cause of DI-ILD [17]. In rheumatoid arthritis, there is an increase in the incidence of methotrexate lung and of tuberculosis following treatment with anti-TNF agents, as these drugs are commonly used now [12]. In contrast, gold lung and the complications of penicillamine have decreased in frequency as these drugs are less in use nowadays. Novel chemotherapeutic agents (e.g. gemcitabine, irinotecan) and drugs used for targeted therapy of hematologic and solid malignancies (e.g. gefitinib, imatinib) were recently shown to produce ILD.

The incidence of DI-ILD ranges from about 1/100,000 for nitrofurantoin, to several percent for amiodarone and >40% for high-dose nitrosourea-based chemotherapy for the treatment of high-risk breast cancer, especially if radiation therapy is used concomitantly. Accordingly, DI-ILD can place a significant limitation on the management of cancer or heart conditions.

Drugs which most often cause ILD include amiodarone, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic agents (e.g. bleomycin, busulfan, chlorambucil, cyclophosphamide, methotrexate, mitomycin, nitrosoureas) and nitro drugs (nitrofurantoin, nilutamide) [1]. Biological agents such as cytokines and growth factors (e.g. colony-stimulating factors, interferons) and proteins (e.g. plasma fraction, intravenous immunoglobulins, antithymocyte globulin) can also produce lung injury [1]. Recently, all-transretinoic acid, docetaxel, gefitinib, gemcitabine, irinotecan and vinorelbine were also implicated. Table 2 shows a summary of the drugs that cause ILD and the resulting clinical radiographic and pathologic patterns.

Table 2. Drugs causing ILD, and the resulting clinical radiographic and pathologic patterns (see text for definitions of the patterns of ILD)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
Abacavir																						1	
Abciximab																	1						
Acebutolol		2			2													3					
Acetaminophen			1																				
Acetylsalicylic acid (aspirin)			1											3	1		1			1		1	
Acitretin	1																						
Acyclovir		1																					
Adrenalin (epinephrine)														2									
Albumin														1									
Allopurinol																				1			
Aminoglutethimide			(1)																				
Amiodarone		4	1		3		3					2			2		1	2					
Amitriptyline			1											1	1								
Amphotericin B					1									2	2								
Ampicillin		1	1																				
Amrinone		1																					
Anagrelide	1																						
ACEIs		1	2															2					
Antazoline		1																					
Antithymocyte globulin							1						1	2									
Atenolol		1																	1				
Aurothiopropanosulfonate (gold salt)	2	2	2	2	1		2																
Azapropazone		1																					
Azathioprine		2															1						
Azithromycin			1																	1			
Barbiturates					1																		
BCG therapy (intravesical)	3	2		2/3											1								3
Beclomethasone			1																				2
Bepridil							1																
Betaxolol					1																		
Bicalutamide		1	1																				
Bleomycin		3	2		3		3	2				3			3				1				
Blood transfusions														3	2								
Bromocriptine							2																

A = Acute ILD/NSIP; **B** = subacute ILD/NSIP; **C** = PIE; **D** = granulomatous ILD; **E** = OP; **F** = DIP; **G** = pulmonary fibrosis; **H** = 'shrinking lung'; **I** = subclinical involvement; **J** = diffuse calcifications; **K** = lipoid pneumonia; **L** = lung nodules; **M** = transient infiltrates; **N** = pulmonary edema; **O** = ARDS; **P** = HUS; **Q** = DAH; **R** = DI-SLE; **S** = PVOD; **T** = pulmonary or systemic vasculitis; **U** = fat embolism; **V** = DIHSS; **W** = opportunistic infections.

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Table 2 (continued)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
Bucillamine			1																				
Buprenorphine														2									
Busulfan		1				1	3												1				
Camptothecin			1											1	2								
Captopril		1	1																				
Carbamazepine	2	2	2		1							1		1			1	1				2	
Carbimazole																				1			
Carmustine (BCNU)		2					3								3				1				
Cefotiam			1																				
Celiprolol	1																						
Cephalexin			1																				
Cephalosporins			1		1																		
Chlorambucil		1					2								1								
Chlorhexidine															1								
Chloroquine			1																				
Chlorozotocin (DCNU)							1																
Chlorpromazine			1											1				1					
Chlorpropamide			1																			1	
Cladribine			1																				
Clindamycin			1																				
Clofazimine									1														
Clofibrate			1															1					
Clomiphene														2	1								
Clonidine																		1					
Clopidogrel																	1						
Clozapine		1	1																				
Colchicine														1								1	
Contraceptives (oral)																		1	1				
Cotrimoxazole	1	1	1											1								1	
Cromoglycate			1																				
Cyclophosphamide		2			1		2							1	2								2
Cyclosporine		1									1			1			1						2
Cyproterone acetate		1	1																				
Cytosine arabinoside														2	2		1						
Danazol							1																
Dapsone			1																			1	
Deferoxamine														1	1								
Desipramine			1																				
Dextran 70														1			1						
Diclofenac			1																				
Diflunisal			1																	1			
Dihydroergocryptine		1			1																		
Dihydroergotamine					1																		
Diltiazem														1									
Dimethylsulfoxide																	1						
Docetaxel	1	1											1	1	1		1						
Dothiepin		1					1																
Efavirenz																						1	
Epoprostenol (see prostacyclin)														1									
Ergometrine														1									
Ergotamine		1					1																
Erythromycin			1											1	1					1			
Etanercept																		1					1
Ethambutol			1																				
Ethchlorvynol														2									
Etoposide		1												1									
Etretinate															1								
Febarbamate			1																				
Fenbufen			1																				
Fenfluramine/dexfenfluramine		1	1																				
Fenoprofen			1																				
Fibrinolytics (including rTPA)																	2						
FK506					1																		
Flecainide		2																					
Floxuridine		1																					
Fludarabine	1	1													1		1						
Fluoresceine														1									
5-Fluorouracil							1								1								

Table 2 (continued)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
Fluoxetine		1																				1	
Flutamide		1																					
Fluvastatin															1			1					
Fosinopril			1																				
Fotemustine							1								2								
Furazolidone			1																				
G/GM-CSF		1	1										2		2								
Gemcitabine		1													2								
Glafenine			1																				
Glibenclamide		1																				1	
Haloperidol															1								
Heparins															2		1						
Heroin		1												3									
Hexamethonium (discontinued)					(3)																		
Hydralazine/dihydralazine		1			1												1	2					
Hydrochlorothiazide		1	1											3	2								
Hydroxyquinoline		1																					
Hydroxyurea		1																					
Ibuprofen			1											1									
Ifosfamide		1					1							1	1								
Imipramine			1																				
Intravenous immunoglobulins														1	1								
Indinavir															1								
Indomethacin			1																				
Infliximab																							2
Insulin														1									
Interferon-α		1		1	1	1																	
Interferon-β		1			1																		
Interleukin-2			1											3	2								
Irinotecan		1												2	2								
Isoniazid			1															2					
Isotretinoin			1																				
Ketamine														1									
Labetalol			1				1											2					
L-asparaginase														2									
L-dopa																		1					
Leukotriene antagonists			1																	2			
Leuprorelin		1													1								
Levofloxacin			1																				
Lidocaine														1									
Intravenous lipids															1						1		
Lomustine (CCNU)		1					2								2				1				
Loxoprofen			1																				
Maprotiline		1	1																				
Mecamylamine					(2)																		
Mefloquine		1													1								
Melphalan		1					2																
Mephenesin			1																				
6-Mercaptopurine		1																					
Mesalamine/mesalazine			2		2																		
Metapramine		1																					
Metformine		1																					
Methadone														1									
Methotrexate	4	3	1	4			1							2	2		1						3
Methyldopa																		2					
Methylphenidate			1																	1			
Methysergide							1[1]																
Metronidazole			1																				
Miconazole															1								
Minocycline			3		1			1				1		1				2		1		2	
Mitomycin C		1					2							2	2	3	2						
Mitoxantrone		1																					
Montelukast			1																	2			
Moxalactam																	1						
Mycophenolate mofetil							1								1								
Nadolol		1																					
Nafazoline														1									
Nalbuphine														1									

➤

Table 2 (continued)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
Nalfon			1																				
Nalidixic acid		1	1															1					
Naloxone														1									
Naproxen			2																				
Nevirapine																						1	
Niflumic acid			1																				
Nilutamide	1	3	1		1																		
Niridazole			1																				
Nitric oxide														1									
Nitrofurantoin	4	3	1		1	1	2	1	1				2	1	1		1	1		2		1	
Nitroglycerin														1									
Nitrosoureas		2					3								2				1				
Nomifensine		1	1																	1			
NSAID			3											1								2	
Noramidopyrine (metamizole)														1									
Estrogens																			1				
OKT3															1								
Olsalazine																		1					
Opioids (morphine agonist/ antagonist)														3									
Oral anticoagulants																	2						
Ornipressin														1									
Oxprenolol		1																					
Oxyphenbutazone		1																					
Paclitaxel		1	1										1										
Para(4)-aminosalicylic acid			2											1									
Paraffin (mineral oil)											4												
Parenteral nutrition																					2		
Penicillamine		2	1		1		1								1		2						
Penicillins			2																	1			
Pentamidine			1																				
Perindopril			1																				
Phenylbutazone			1											1								1	
Phenylephrine														1									
Phenytoin		2	2		1							1					1	1		1		1	
Pindolol							1											1					
Piroxicam			1																				
Pituitary snuff		1		1																			
Plasma (fresh frozen)														2									
Practolol (recalled)		(1)					(1)																
Pranlukast	1																			1			
Pranoprofen			1																				
Pravastatin					1																		
Procainamide		1																2					
Procarbazine	1	1	1				1																
Propofol													1								1		
Propoxyphene														1									
Propranolol			1											1				2					
Propylthiouracil		1	1									1			1		1			2			
Prostacyclin														2									
Protamine														1	1								
Pyrimethamine-dapsone			1																			1	
Pyrimethamine-sulfadoxine		1	1											1									
Quinidine		1															1	1					
Radiation therapy	2	2			2		4	2	2						2				2				1
Radiographic contrast media			1											2	2		1						
Raltitrexed		1																					
Retinoic acid													1	2	2		2						
Rifampin			1																				
Ritodrine														3									
Rituximab						1																	
Roxithromycin			1																	1			
Salbutamol (injected)														3									
Serrapeptase			1																				
Sertraline			1																				
Simvastin		1	1		1										1			1					
Sirolimus (rapamycin)		1															1						
Sotalol					1																		

Table 2 (continued)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
β-2 agonists (administered i.v. in obstetrics and gynecology)														3									
Steroids																							3
Streptokinase															1		2						
Streptomycin			1																				
Sulfamides-sulfonamides		1	2											1	1			1		2			
Sulfasalazine		1	2			1	1							1				1		1			
Sulindac			1	1																		1	
Tacrolimus					1																		
Tamoxifen							1							1									
Tenidap			1																				
Terbutaline														3									
Tetracycline			2															2					
Thalidomide		1																					
Tiaprofenic acid			1																				
Ticlopidine			1		1																		
Tiopronin		1																					
Tirofiban																	1						
TNF-α														2			1						
Tocainide		1					1																
Tolazamide			1																				
Tolfenamic acid			1																				
Topotecan					1								2		2								
Tosufloxacin			1																				
Trazodone			1																				
Triazolam														1									
Tricyclic antidepressants														2									
Trimipramine			1																				
Troglitazone														1									
Troleandomycin			1																				
L-tryptophan			(4)		(1)															(4)			
Urokinase																	2						
Valproate																	1						
Valsartan		1																					
Vasopressin														1									
Venlafaxine			1																				
Vinblastine												1		1	1								
Vindesine	1														1	1							
Vinorelbine														1									
Vitamin D										1													
Zafirlukast			1																	1			

Drugs which cause pulmonary edema or ARDS may cause transient pulmonary infiltrates in some patients. Figures indicate the frequency of the adverse effect, from 1 (rare) to 4 (common). Empty cells indicate that this adverse effect has not been reported. Parentheses around figures indicate that the drug has been recalled (e.g. hexamethonium, practolol). When most drugs in a therapeutic class induce similar adverse effects in the lung (e.g. ACEIs, β-blockers, β-2 agonists, leukotriene antagonisis, NSAIDs), the family of drugs is mentioned, not all particular drugs in the class.

[1] The pulmonary fibrosis of methysergide and of other ergots is associated with pleural fibrosis, the predominant adverse effect from these drugs.

In general, drug-induced pulmonary toxicity occurs during rather than after treatment with the drug, more often via the oral or parenteral route. Less frequently, drugs produce ILD following inhaled, topical (ophthalmic, dermal, intanasal), intrathecal, intracavitary and intra-arterial administration. Rarely, ILD occurs after an overdose of the drug (e.g. anticoagulant-induced alveolar hemorrhage, aspirin- or tricyclic antidepressant-induced pulmonary edema). Sometimes, ILD is explained by the pharmacologic action of the drug (e.g. the dyslipidosis induced by amiodarone, or alveolar hemorrhage produced by oral anticoagulants). More commonly, however, DI-ILD occurs with normal doses of the drug, and develops unexpectedly as an idiosyncratic reaction in a few patients. This makes early detection and prevention of drug-induced diseases difficult.

Some drugs cause a stereotypical pattern of involvement. For instance, minocycline produces an eosinophilic

Table 3. Patterns of lung involvement on imaging, drugs which produce the patterns and histopathologic correlates in DI-ILD (see Pneumotox [1])

Pattern on HRCT and imaging	Typical drugs causing the pattern	Histopathological correlates
Intralobular thickening	chemotherapeutic agents, amiodarone drugs which produce pulmonary edema	interstitial pulmonary edema, DAD
Smooth interlobular thickening	chemotherapeutic agents drugs which produce PIE drugs which produce pulmonary edema	interstitial pulmonary edema, DAD, eosinophilic pneumonia
Irregular interlobular thickening	drugs which produce pulmonary fibrosis	pulmonary fibrosis
Micronodular opacities	BCG, methotrexate	granulomas
Macronodular opacities	amiodarone, bleomycin	amiodarone pneumonitis, OP
Ground-glass pattern	drugs which cause cellular interstitial pneumonia (see Pneumotox [1])	cellular interstitial pneumonia (alveolitis)
Smooth mosaic lung attenuation	drugs which cause cellular interstitial pneumonia (see Pneumotox [1]) drugs which produce DAH	cellular interstitial pneumonia alveolar hemorrhage with or without capillaritis
Sharply demarcated mosaic with low lung attenuation	nitofurantoin mineral oil (paraffin)	desquamative interstitial pneumonia lipoid pneumonia
Diffuse alveolar opacities with or without the batwing pattern	drugs which produce pulmonary edema, DAD, alveolar hemorrhage, or cellular interstitial pneumonia	pulmonary edema, DAH, dense cellular interstitial pneumonia or DAD
The photographic negative of pulmonary edema or the reverse of the batwing pattern	drugs which produce PIE	eosinophilic pneumonia
Patchy or diffuse opacities with increased attenuation	amiodarone	amiodarone pneumonitis
Patchy opacities along bronchovascular bundles	nitrofurantoin, nilutamide	OP
Localized consolidation	drugs which produce OP or PIE	OP or eosinophilic pneumonia
Migratory opacities	drugs which produce OP or PIE	OP or eosinophilic pneumonia
Localized honeycombing	radiation therapy, amiodarone	localized pulmonary fibrosis and honeycombing
Diffuse honeycombing	chemotherapeutic agents, amiodarone	diffuse pulmonary fibrosis and honeycombing
Tree in bud	aspiration of drugs (e.g. kayexalate resin)	bronchiolitis

pneumonia [18, 19], and methotrexate causes an acute granulomatous ILD which mimics an opportunistic infection [6]. In contrast, other drugs (e.g. amiodarone, bleomycin) can produce a constellation of patterns, including pulmonary infiltrates and an asymptomatic state, nonspecific interstitial pneumonia, PIE, OP, multiple lung nodules, an adult respiratory distress syndrome (ARDS) picture and irreversible pulmonary fibrosis. Most drugs of a class may induce a similar pattern of pulmonary involvement, suggesting a common cytopathic mechanism. For instance, most NSAIDs can produce PIE, and the vast majority of alkylating agents produce a DAD picture or pulmonary fibrosis [1]. Cross-reactivity has rarely been documented with drugs causing ILD. This contrasts with drug-induced allergic and anaphylactic reactions, where cross-sensitivity is common. Thus, resuming treatment with a drug which is chemically related to the one that produced the ILD is generally considered safe. Anticonvulsants, statins and chemotherapeutic drugs are notable exceptions, as further treatment with a drug congener may aggravate or exacerbate the ILD.

Clinical Patterns of DI-ILD

Acute ILD with Respiratory Failure

DI-ILD can produce acute widespread pulmonary infiltrates with life-threatening respiratory failure. This may correspond to the following clinicopathologic patterns of involvement:

- Acute cellular interstitial pneumonia (e.g. with chrysotherapy, β-blockers and nitrofurantoin), pulmonary granulomatosis [e.g. with methotrexate, interferon and *Bacillus* Calmette-Guérin (BCG) therapy], eosinophilic pneumonia (e.g. with minocycline and NSAIDs), OP (e.g. with interferons, nitrofurantoin and statins) or the acute variant of APT [1].
- DAD (e.g. with chemotherapeutic agents and aspirin) [5].
- Pulmonary edema (e.g. with aspirin, hydrochlorothiazide, blood transfusions, tricyclic antidepressants and illicit drugs) [20].
- Diffuse alveolar hemorrhage (DAH) (e.g. with anticoagulants and inhibitors of platelet IIB/III receptors) [21].

Overall, acute drug-induced respiratory failure more often results from treatment with methotrexate, minocycline, antidepressants, β-2 receptor agonists, chemotherapeutic agents, amiodarone and transfusion of blood and blood fractions [1]. Patients with moderately severe DI-ILD may end up with acute respiratory failure if the drug etiology is not recognized in time and the drug is continued. Patients with acute DI-ILD present with the progressive or rapid onset of dry cough, high fever, dyspnea and pulmonary infiltrates culminating in acute hypoxemic respiratory failure or an ARDS picture. These patients often require admission to the intensive care unit and mechanical ventilation. They are often too ill to undergo detailed evaluation of lung function, beyond simple measurements of arterial blood gases. On imaging, early stages show linear shadows, inter- and intralobular opacities and a ground-glass or miliary pattern [3, 22, 23] (table 3). Later, development of dense diffuse opacities on air bronchograms and volume loss occur. Pleural effusion is an occasional associated finding in methotrexate lung and in acute eosinophilic pneumonia.

In general, it is difficult to infer the histopathologic background of drug-induced parenchymal reactions from imaging. It is also difficult to separate the drug condition from an opportunistic infection, as both conditions may produce the same pattern of involvement on imaging. The diagnosis of drug-induced hypersensitivity pneumonitis, eosinophilic pneumonia and chemotherapy lung is aided

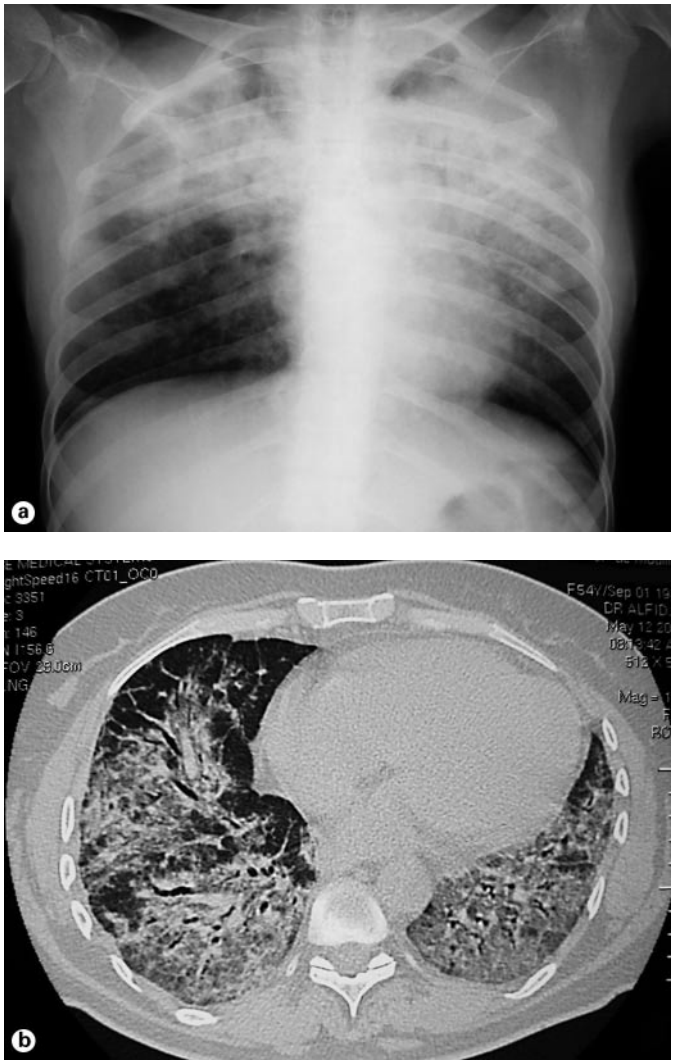

Fig. 1a, b. Acute methotrexate lung. Methotrexate produces an acute granulomatous pneumonia mimicking an infection which must be ruled out by appropriate techniques.

when there is an increase in BAL lymphocytes, eosinophils and dysplastic type II cells, respectively [14]. Macroscopically, in alveolar hemorrhage, the BAL is hemorrhagic and demonstrates increased staining in successive aliquots. BAL is also helpful to rule out an infection, notably in patients on immunosuppressive drugs. In selected cases, an open lung biopsy is required to confirm the diagnosis of DI-ILD. Examination of lung tissue can rule out involvement of the background disease or an infection, and help diagnose a drug-induced condition if a pattern consistent with the particular drug is found.

Acute methotrexate lung (fig. 1) typifies acute drug-induced cellular interstitial pneumonia [24–26]. The con-

dition develops after variable time into treatment. It occurs in 0.3–11.6% of patients receiving the drug for the treatment of inflammatory conditions, mainly rheumatoid arthritis, or hematologic malignancies. Recognized risk factors include diabetes, hypoalbuminemia, rheumatoid lung involvement, use of disease-modifying drugs and advanced age. Full-blown disease is preceded by a dry cough, dyspnea, fever and a normal chest radiograph for a few days or 1–2 weeks. The cough must be differentiated from lone methotrexate-induced cough, which does not evolve to methotrexate lung, and may disappear despite continued exposure to the drug [27]. After a prodromal period of a few days to 1–2 weeks, methotrexate lung accelerates, producing rapidly progressive, dense, diffuse alveolar shadowing and volume loss [24]. The diagnostic criteria of Clearkin et al. [28] include dyspnea of acute onset, fever above 38°C, respiratory rate greater than 28/min, the presence of radiographic abnormalities, a white blood cell count above 15,000/μl, negative blood and sputum or BAL sampling and cultures, a restrictive lung function defect with reduced diffusing capacity for carbon monoxide, $PaO_2 < 50$ mm Hg on room air, and evidence of ILD on a lung biopsy specimen. The disease is deemed definite, probable or possible if 6, 5 or 4 criteria are fulfilled, respectively [28]. BAL can be performed in most patients with methotrexate lung, if provision is made to correct the hypoxemia which almost invariably occurs during the procedure. BAL shows elevated CD4+ or CD8+ lymphocyte counts depending on the time into the disease and the use of corticosteroid drugs [14, 29]. It is essential to rule out an opportunistic infection using BAL, as opportunistic pneumonias are very similar to methotrexate lung, with no real clinical or radiological discriminators, and because infection with *Pneumocystis jiroveci*, cytomegalovirus, *Cryptococcus*, herpes zoster and *Nocardia* have been particularly associated with treatment with methotrexate, especially if CD4+ lymphocytes are below 150/μl during treatment, or cumulated doses of methotrexate are above 700 mg [30]. *Pneumocystis* pneumonia with low microorganism counts may be particularly difficult to distinguish from methotrexate lung.

Histological findings were available in 49 of 123 reports on methotrexate lung reviewed by Imokawa et al. [25], and indicated interstitial inflammation, fibrosis, small ill-defined granulomas and increased tissue eosinophils in 71, 59, 35 and 18% of cases, respectively. However, blood or tissue eosinophilia are not a predominant feature in methotrexate pneumonitis. In predominantly granulomatous methotrexate lung, the involvement is patchy, with intervening areas of normal tissue, or tissue showing moderate cellular interstitial pneumonia [25]. Type 2 cell hyperplasia is a notable feature of methotrexate lung, but this feature is less prominent than with other chemotherapeutic or alkylating agents. Alveolar edema, DAD and DAH characterize those cases with severe hyperacute disease. Drug withdrawal and high-dose intravenous corticosteroid therapy are usually associated with a favorable outcome. The chest radiograph, CT and pulmonary function improve over a few weeks, and normalize after several months with no relapse if the patient is not rechallenged [26]. However, a mortality rate of 15% in a recent series underlines the need for careful management of this condition [31]. Although in some patients, the disease did not relapse following rechallenge, reexposure is contraindicated, as relapse and death may ensue [31].

Several of the features that characterize acute methotrexate lung, except granulomas, are found in gold lung [32]. The condition also has an acute course, produces diffuse infiltrates with respiratory failure and cellular interstitial pneumonia on histology, and responds to drug withdrawal and corticosteroid therapy. There is lymphocytosis in the BAL, and gold lung may simulate an infection. Rechallenge with the drug also produces relapse of the disease. Overall, however, gold lung has a less severe course than methotrexate lung.

Nitrofurantoin and interferon-α may also produce an acute cellular interstitial pneumonia pattern with respiratory failure [1]. Cavitary BCG therapy can produce an acute granulomatous pneumonia with alveolar damage [33].

Drug-induced acute eosinophilic pneumonia (fig. 2) is sometimes difficult to distinguish from drug-induced cellular interstitial pneumonia, both clinically and on imaging [19]. Drugs causing acute eosinophilic pneumonia include amitryptiline, chloroquine, fludarabine, infliximab, interleukin-2, minocycline, sertraline, troleandomycin and tryptophan, among others [1]. Most cases of drug-induced eosinophilic pneumonia, however, are described in young people during chronic treatment with minocycline for acne vulgaris [18]. On imaging, there are dense bilateral linear or alveolar opacities, and bilateral pleural effusion or lymph node enlargement may be present as associated features. Acute eosinophilic pneumonia is diagnosed by eosinophilia in the blood, BAL and lung tissue. BAL is an essential and minimally invasive diagnostic tool in this condition. A lung biopsy is rarely needed for the diagnosis of this condition. Eosinophils can be suppressed by corticosteroid drugs. There may be overlapping histopathologic features of eosinophilic pneumonia

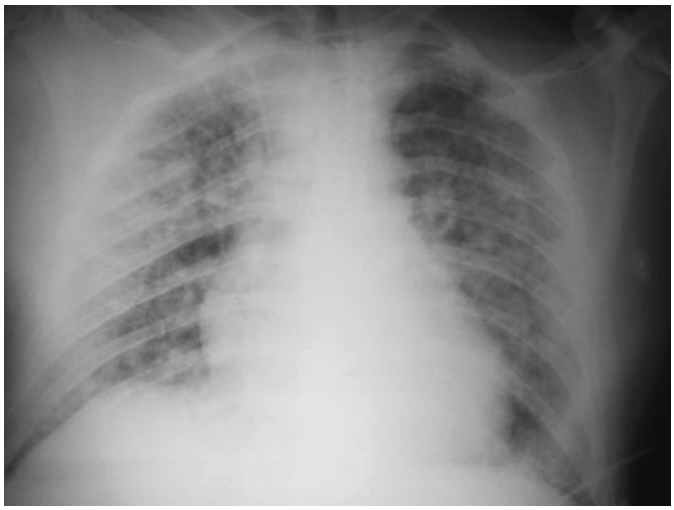

Fig. 2. Acute eosinophilic pneumonia due to minocycline in a young patient producing diffuse alveolar opacities and acute respiratory failure. Eosinophilic pneumonia is difficult to separate on imaging from acute noneosinophilic pneumonias (see fig. 1). However, eosinophils are increased in the BAL in eosinophilic pneumonia.

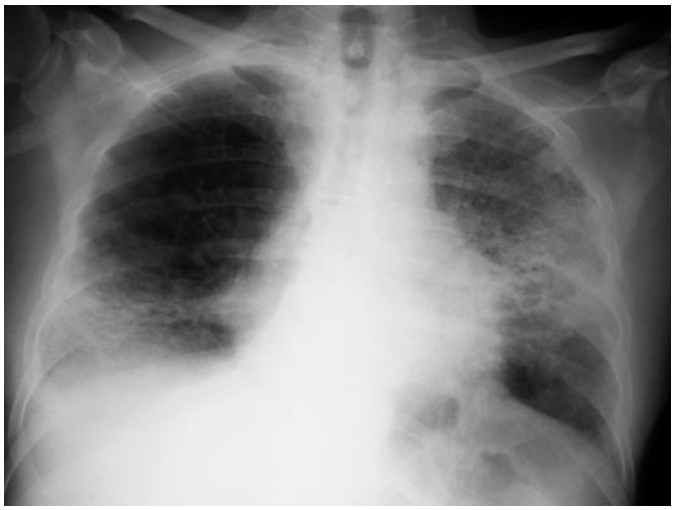

Fig. 3. Acute chemotherapy lung with DAD due, in this particular case, to the combination of radiation therapy to the chest and mitomycin for the treatment of lung and bladder cancer.

and OP or, sometimes, Churg-Strauss vasculitis. Drug-induced acute eosinophilic pneumonia generally responds to drug withdrawal and corticosteroid therapy, but tends to relapse if the patient is rechallenged with the drug.

Chemotherapy (fig. 3) lung is a severe pulmonary reaction that develops during or shortly after treatment with chemotherapeutic agents including antibiotics (bleomycin, mitomycin C), alkylating agents (busulfan, cyclophosphamide, chlorambucil, melphalan), antimetabolites (methotrexate, 6-mercaptopurine, azathioprine, cytosine arabinoside, gemcitabine, fludarabine), nitrosamines [bischloroethyl nitrosourea (BCNU), chloroethylcyclohexyl nitrosourea] and podophyllotoxins (etoposide, paclitaxel, docetaxel) [5]. Recently, all-transretinoic acid, gefitinib, imatinib, irinotecan, interferon-gamma, interleukin-2 and TNF-α were also shown to cause the syndrome [1]. Rarely, the condition results from the administration of noncytotoxic agents (e.g. aspirin, nitrofurantoin) [1]. Chemotherapy lung corresponds histologically to DAD, edema and early fibrosis and occurs more frequently and is more severe in patients receiving high-dose or multiagent chemotherapy, compared with treatment with a single agent. Concurrent radiation or oxygen therapy increases the risk of developing this condition. Lung cancer patients on a second- or third-line chemotherapy regimen may also be at increased risk. Sometimes, chemotherapy lung develops on a background of prior mild or unresolved chemotherapy- or radiation-induced damage, and is triggered by further treatment or occurs as a preterminal event. Acute chemotherapy lung must be differentiated from overload pulmonary edema, chemotherapy-induced vascular leak syndrome and opportunistic infections [5]. Tools used to distinguish between these conditions include diuresis, BAL, a trial of corticosteroids and lung biopsy. Chemotherapy lung manifests with dyspnea, diffuse pulmonary infiltrates, volume loss and respiratory failure which is only mildly responsive to treatment with corticosteroid drugs. On imaging, the density of pulmonary infiltrates ranges from a diffuse haze or ground-glass pattern, to white lungs [3, 34]. On high-resolution CT (HRCT), a ground-glass pattern, linear opacities, inter- or intralobular thickening and alveolar shadows are described. Histopathologic appearances include DAD with hyaline membranes, marked dysplasia of type 2 pneumocytes, interstitial or alveolar edema, and early fibrosis.

Determining the histopathologic background of pulmonary infiltrates in patients who develop severe involvement while receiving chemotherapeutic agents is problematic, as involvement of the background disease, drug- or radiation-induced ILD, pulmonary edema, alveolar hemorrhage or an infection can be undistinguishable from drug-induced DAD, and a confirmatory lung biopsy is often not available due to the severity of the underlying condition, or because of respiratory failure. Institution of corticosteroid therapy may be followed by transient improvement, especially if the disease has a recent onset.

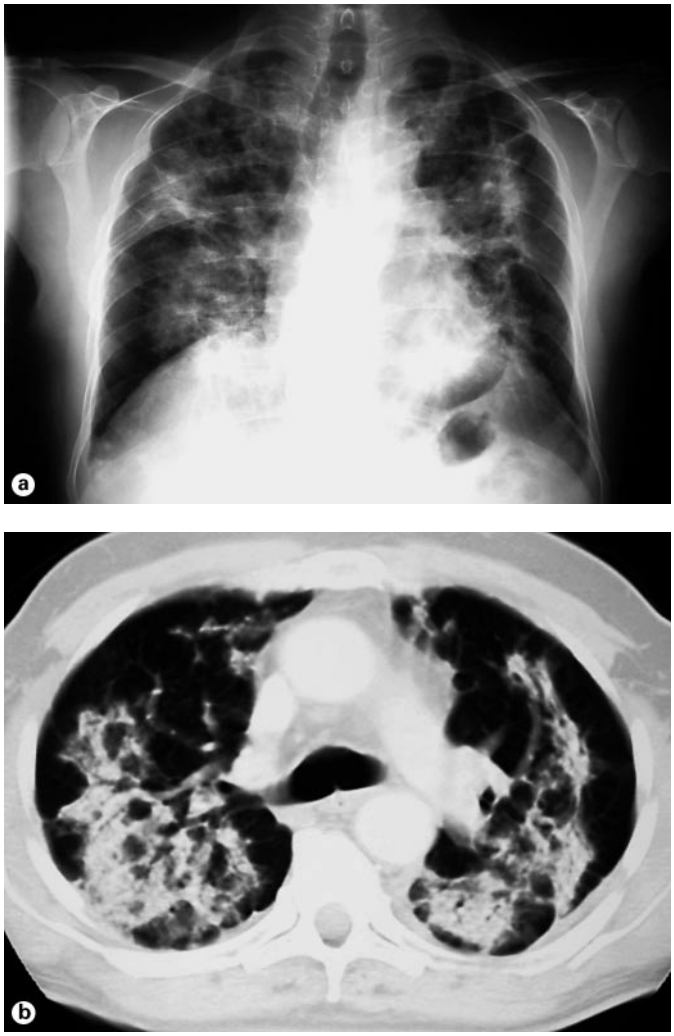

Fig. 4a, b. Subacute cellular interstitial pneumonitis due, in this case, to methotrexate. There are dense patchy alveolar shadows on CT.

Overall, however, the response to treatment and the prognosis of this condition are poor. Chemotherapy lung may negatively impact on the management of the underlying disease if a change in therapy to less efficacious drugs is required. In a few survivors, irreversible lung fibrosis may develop, requiring specific management, including, in some, lung transplantation.

Acute APT is an unusual pattern of lung response to amiodarone [17, 35–38]. Acute APT may occur within a few days after a loading dose of intravenous amiodarone, or later at almost any time into treatment. Sometimes acute APT develops after cardiac or pulmonary surgery, or following implantation of an automatic defibrillator [17]. Anesthesia, oxygen and/or mechanical ventilation may synergize APT. Surgical patients with a recent history of resection for lung cancer are at greater risk, as they have a combination of a frequent need for amiodarone to control postoperative arrhythmias, poor ventilatory reserve due to the recent lung resection, and a background of smoking, chronic obstructive pulmonary disease (COPD) or emphysema [39]. Routine use of amiodarone in this setting is discouraged.

Acute APT manifests with dyspnea and diffuse interstitial, alveolar or mixed shadows, with volume loss, severe hypoxemia or an ARDS picture. Atypical pulmonary edema, thromboembolism or infarction, lung cancer and a coincidental infection must be carefully ruled out. If diuresis, measurement of lung function and appropriate imaging techniques do not enable this distinction, cardiac echography, measurement of pulmonary capillary wedge pressure, BAL and, in selected cases, a lung biopsy are required. Histopathological findings in acute APT include diffuse or resolving DAD, interstitial edema and fibrosis, superimposed on a background of more classic changes suggesting APT such as dyslipidosis with accumulation of foamy alveolar or interstitial cells. The mortality in acute APT approaches 40–50%, despite drug withdrawal and corticosteroid therapy.

Drug-induced pulmonary edema is a complication of treatment with several chemically unrelated drugs and procedures, including narcotic analgesics, aspirin and other NSAIDs, high-dose intravenous β-2 agonists, blood transfusion [this complication is known as 'transfusion-related acute lung injury' (TRALI)], colchicine, cyclophosphamide, epinephrine, hydrochlorothiazide, methotrexate, nitrofurantoin, noramidopyrine, opiates, quinine, radiographic contrast material and vasopressin, among others [1, 20]. Incidence rates and mechanisms of the edema differ between drugs. Pulmonary edema is also a complication of *overdoses* of tricyclic antidepressants [40] or heroin ('heroin lung') [7]. Pulmonary edema can complicate treatments with nifedipine, prostacyclin or nitric oxide, when these drugs are used to treat pulmonary hypertension [1]. Pulmonary edema can also develop as a complication of hyperacute gold, nitrofurantoin and methotrexate pneumonitis [1]. Pulmonary edema related to vascular leak syndrome is a complication of treatment with interleukin-2 and novel chemotherapeutic agents [1, 41]. Contrasting with other DI-ILD, pulmonary edema can develop very rapidly (within a minute) after drug administration, or later into treatment (e.g. with hydrochlorothiazide or aspirin). Pulmonary edema manifests with dyspnea, diffuse pulmonary infiltrates and respira-

tory failure or an ARDS picture. Rarely, a foamy tracheal exudate confirms the diagnosis. Most cases of drug-induced pulmonary edema are noncardiac, and result from a drug-related increase in pulmonary capillary permeability. This is confirmed by the normalcy of heart size on imaging, and of cardiac echocardiography and capillary wedge pressure measurements. Histopathologic appearances include bland edema, with proteinaceous fluid in the alveolar space, coexisting with a normal or moderately edematous interstitium. Management of drug-induced pulmonary edema includes drug discontinuation and, in some patients, positive pressure breathing or mechanical ventilation. Diuretic drugs may detrimentally influence drug-induced pulmonary edema, as the combined effect of vascular leak and diuretics may cause systemic hypotension and vascular collapse. The role of corticosteroids in this condition is unclear. Pulmonary edema generally improves quickly after drug dechallenge. Rechallenge with the drug causes recurrence of all manifestations of the disease.

Drug-induced DAH consists of diffuse and synchronous bleeding from the pulmonary microcirculation, with or without demonstrable pulmonary capillaritis [21]. Drug-induced DAH occurs in isolation, or in association with involvement of the kidney or other organs suggesting drug-induced systemic micropolyangiitis [12]. BAL is an efficient and minimally invasive tool for the diagnosis of DAH. Therefore, a lung biopsy is rarely performed in patients with this condition, and histopathologic features are partially elucidated. Drugs causing DAH include abciximab, anticoagulants, fibrinolytics, allopurinol, aspirin, all-transretinoic acid, azathioprine, clopidogrel, methotrexate, nitrofurantoin, phenytoin, propylthiouracil, retinoic acid, sirolimus and tirofiban [1]. Drugs causing thrombocytopenia can also produce bleeding in the lung. Occasionally, DAH occurs as a complication of acute pneumonitis from treatment with gold, methotrexate or nitrofurantoin [1]. Drug-induced DAH does not generally occur in drug-induced lupus. Hydralazine, penicillamine, propylthiouracil and, less often, azathioprine, leflunomide and phenytoin can produce a pneumo-renal syndrome with severe AH, which mimics Goodpasture's or Wegener's disease [12, 42]. Patients with AH resulting from treatment with these agents may present with a perinuclear ANCA staining pattern and antimyeloperoxidase, -lactoferrin or -elastase specificity, contrasted with the cytoplasmic ANCA staining pattern and antiproteinase 3 specificity of naturally occurring Wegener's disease. Antiglomerular basement membrane antibodies are rarely found in drug-induced DAH, as

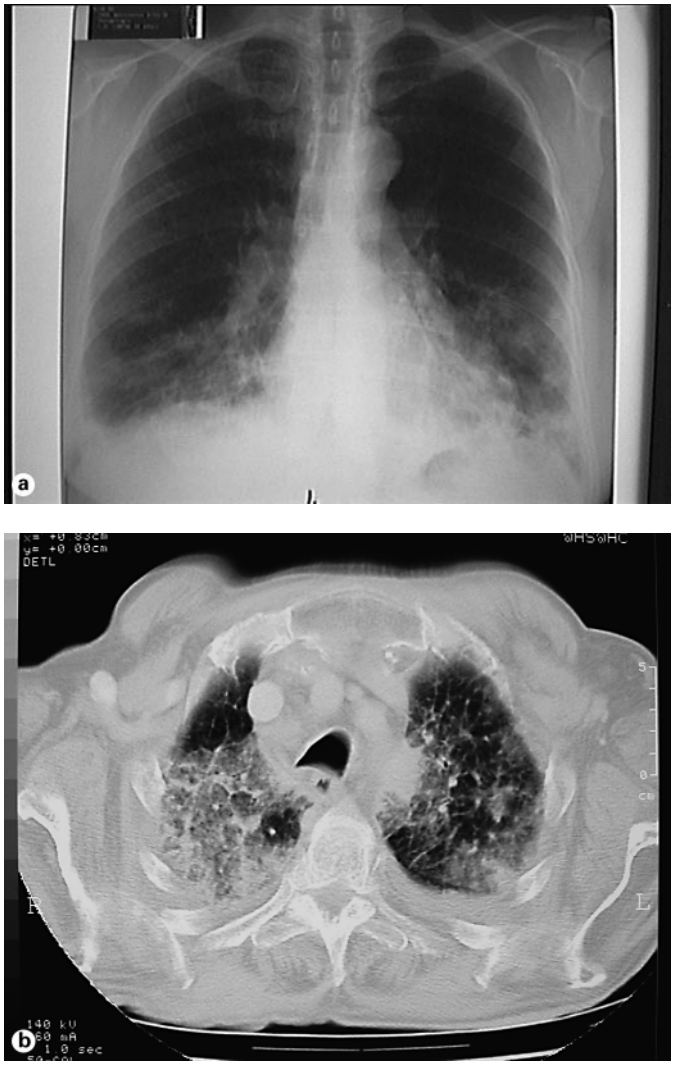

Fig. 5. a The opacities of drug-induced eosinophilic pneumonia may localize anywhere in the lung, or be diffuse or migratory. **b** HRCT shows lobular opacities, interlobular thickening and slight left pleural effusion.

opposed to naturally occurring Goodpasture's disease. Drug-induced AH can be rapidly progressive, and requires expeditious management to avoid irreversible intra-alveolar clotting. Full-blown disease may cause general symptoms, arthralgias, dyspnea, alveolar infiltrates, which may assume a batwing distribution, and anemia. Hemoptysis is not a constant feature, even in patients with significant alveolar bleeding. An increase in the diffusing capacity suggesting free hemoglobin in alveolar spaces has been found in a few patients with DAH and indicates massive bleeding. However, this is not a reliable finding. Macroscopically, BAL demonstrates increased

bleeding in serial aliquots, and microscopically, it shows red cells. In cases with subacute or chronic bleeding, hemosiderin-laden macrophages are present [21]. Testing for ANAs, ANCAs and anti-GBM autoantibodies is essential to classify drug-induced DAH (autoimmune vs. non-autoimmune), and to separate drug-induced DAH from DAH related to a naturally occurring systemic illness [42].

Drug causality is suggested when AH occurs during treatment with drugs which are intended to produce coagulation defects. Otherwise, assessment of causality is more difficult, because AH can occur in so many systemic conditions [43]. Patients who present with AH and positive ANA, especially the anti-double-strand subtype, ANCAs with cytoplasmic staining and PR3 specificity, or anti-GBM antibodies are more likely to have naturally occurring lupus erythematosus, Wegener's or Goodpasture's disease, respectively, rather than a drug-induced condition. A temporal association of drug exposure, perinuclear ANCA titers and AH is consistent with a drug etiology. A change in ANCA specificity in a patient with Wegener's granulomatosis during follow-up may indicate drug-induced disease, rather than relapse of the background condition [44].

Drug withdrawal is advised and may suffice in patients with anticoagulant-induced bleeding. Although no current guidelines exist, patients with severe AH and extensive or persistent bleeding or evidence of multiorgan failure are considered for treatment with corticosteroids or immunosuppressive drugs in a manner similar to autoimmune disease [21].

Circumstantial evidence relates chronic exposure to amiodarone, nitrofurantoin and statins to the development of acute OP or fibrinous OP [45]. This condition is unusual and severe, and is characterized by diffuse pulmonary infiltrates in the context of dyspnea. Diagnosis requires a confirmatory lung biopsy. The condition can also occur sporadically with no identifiable cause. Response to drug withdrawal and corticosteroid therapy is limited, with the majority of patients dying from the condition.

Transfusion of whole blood, platelets, plasma, plasma-derived coagulation factors and immunogobulins can produce the TRALI syndrome [46, 47], which is characterized by severe pulmonary edema. Typically, symptoms develop within a few hours of the transfusion. TRALI must be distinguished from overload pulmonary edema and from ABO or Rhesus incompatibility. Transient hypoxemia during transfusion in mechanically ventilated patients may indicate an attenuated form of TRALI. The syndrome is thought to result from the transfer of complement-activating HLA class I or II granulocyte-specific or lymphocytotoxic antibodies from one donor in the pool of donors from whom the plasma fraction was obtained. The antibodies activate and agglutinate neutrophils, causing pulmonary endothelial damage, vascular leak and pulmonary edema. Other mechanisms for TRALI include the accumulation of platelet activating factor-like substances in stored blood. In 85% of TRALI cases, an antibody is found in one donor, generally a woman with two or more pregnancies. Most patients with TRALI recover within 96 h. However, a fraction of patients die from intractable respiratory failure. Recognition of TRALI is essential and should prompt examination of the donor product and subsequent elimination of the donor from the donor pool [48].

The occurrence of acute dyspnea and pleuritic chest pain has been temporally associated with treatment with antithymocyte globulin, bleomycin, crack cocaine, cyclophosphamide, hydrochlorothiazide, intravenous immunoglobulins, methotrexate, minocycline, nitrofurantoin and statins [1, 49–52]. There is a discrepancy between the intensity of chest symptoms and the extent of pulmonary opacities, which can be minimal on imaging. Acute excruciating chest pain is also described in patients with drug-induced lupus, and can also occur after sclerotherapy of esophageal varices, or following closure of brain arteriovenous malformations with acrylate glue. Patients with drug-induced acute chest pain are generally admitted to the emergency room with a working diagnosis of pulmonary embolism, pericarditis or myocardial infarction, and drug history taking is required in patients who present in this way. The histopathological background of this condition is unclear, with edema, angiitis, cellular pneumonia or OP documented in a few cases. Withdrawal of the suspected drug is followed by rapid reversal of symptoms, which return if the patient is rechallenged.

Subacute/Chronic DI-ILD

All of the above patterns of DI-ILD can exist in a diminutive form if a drug etiology is suspected and the drug is discontinued in time, if the reaction was quenched by corticosteroid therapy or because some drugs inherently produce pulmonary reactions which are milder than those described above (fig. 4).

✻ Many cases of drug-induced cellular interstitial pneumonia have a benign course, with moderate dyspnea, a nonproductive cough, slight fever, vague or patchy pulmonary infiltrates, moderate hypoxemia and, sometimes, changes in liver chemistry which suggest concomitant hepatotoxicity. Drugs and therapies causing a cellular

interstitial pneumonia pattern include angiotensin-converting enzyme inhibitors (ACEIs), β-blocking agents, intracavitary BCG therapy, chlorambucil, chrysotherapy, flecainide, fludarabine, fluoxetine, maprotiline, nitrofurantoin, nilutamide, procainamide, simvastatin, sulfasalazine and, sometimes, methotrexate [1]. Radiographic studies indicate bilateral, roughly symmetric interstitial and/or alveolar infiltrates. A miliary pattern is uncommon, although it has been reported with the use of BCG therapy, chrysotherapy, methotrexate, nilutamide and sirolimus. The infiltrates can be diffuse or localized in the lung bases or mid-lung zones, rather than specifically in the apices. Radiographic density can be a discrete haze or ground-glass pattern, or patchy areas of dense alveolar consolidation. Pleural effusion and mediastinal lymphadenopathy are occasional findings [53]. On HRCT, interstitial septal or intralobular lines, a crazy-paving pattern, areas of increased attenuation, or a ground-glass or mosaic pattern can be present [3, 34]. Restrictive pulmonary function and hypoxemia are usually present, and these correlate with the extent of involvement on imaging. BAL is generally indicated to exclude an infection and to support a drug etiology. It shows a lymphocyte predominance with an increase in CD4+ or CD8+ subsets depending on the drug, the patient, the time at which the BAL is performed and a possible background of corticosteroid therapy [14, 29]. A neutrophilic, mixed lymphocytic and neutrophilic and/or eosinophilic pattern has been reported less frequently [14]. A lung biopsy is rarely needed to confirm the diagnosis of drug-induced cellular interstitial pneumonia, as most cases have a mild course and will respond to drug withdrawal with or without corticosteroid therapy. A risk-benefit analysis of lung biopsy versus conservative management is not available [54]. Histopathologic appearances include cellular interstitial pneumonia, interstitial edema and, sometimes, areas of OP or moderate fibrosis. The prognosis of drug-induced cellular interstitial pneumonia is good. Corticosteroid therapy is indicated in patients with extensive opacities or significant hypoxemia, or in those in whom drug withdrawal fails to translate into definite improvement. The development of lung fibrosis following recognition and treatment of this condition is rare. Rechallenge with the drug often leads to relapse, sometimes with an increase in severity, and instructions should be given to the patient to avoid inadvertent rechallenge.

Desquamative interstitial pneumonia was identified as a rare pattern of response to chronic treatment with nitrofurantoin and, less often, interferon [1, 55].

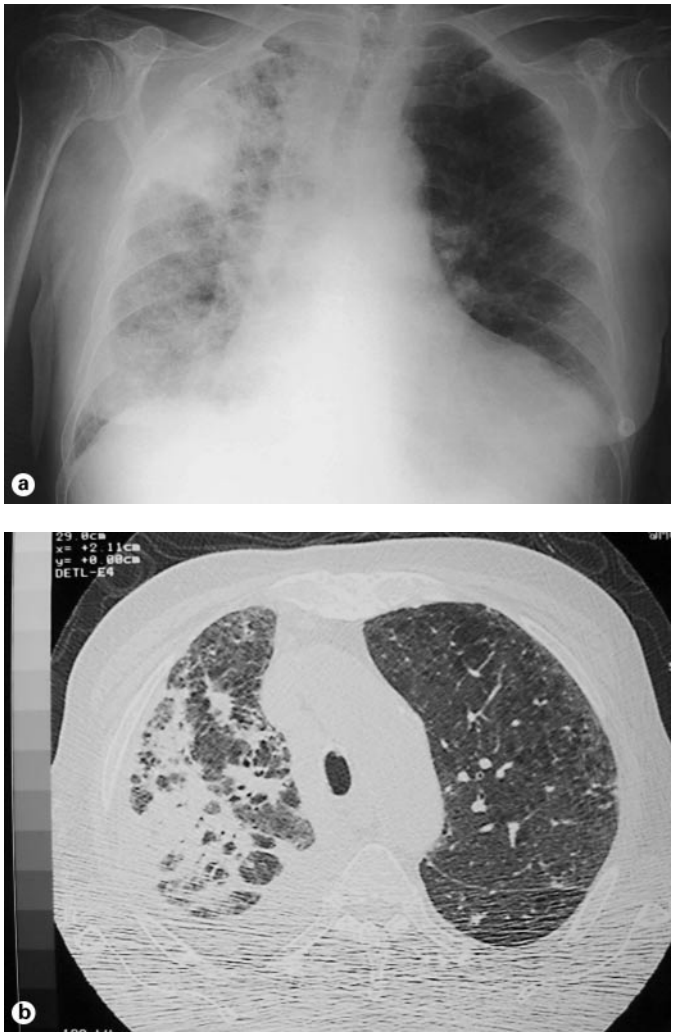

Fig. 6a, b. APT is often asymmetric, and predominant involvement of the right upper lobe is common.

✻ Drug-induced PIE (fig. 5a, b) can be caused by multiple chemically unrelated drugs, including ACEIs, antidepressants (amitriptyline, clomipramine, maprotiline, sertraline, trazodone, venlafaxine), aspirin and other NSAIDs, carbamazepine, chloroquine, interferon, mesalazine, minocycline, inhaled or parenteral pentamidine, phenytoin, pyrimethamine, radiographic contrast material, sulfamides (sulfasalazine, sulfamethoxazole) and *L*-tryptophan, among others [1, 19]. Methotrexate lung is often associated with mild eosinophilia in blood, BAL and lung tissue; however, it is not an eosinophilic pneumonia. Certain drug *classes* as a whole (e.g. antibiotics, antidepressants, ACEIs, NSAIDs) can cause PIE. Rarely, the clinical and pathological features of PIE may overlap with the Churg-Strauss syndrome, and distinguishing the

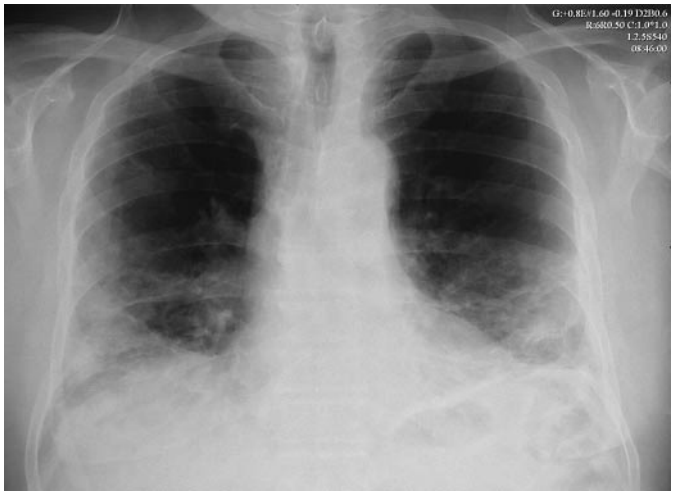

Fig. 7. The opacities in pulmonary fibrosis often predominate in the lung bases, as in this case of mitomycin-induced pulmonary fibrosis.

two conditions can be problematic in the absence of lung tissue available for review. Leukotriene receptor antagonists can produce both conditions. Patients develop drug-induced PIE after variable time into treatment. Drugs administered topically or via inhalation cause PIE less often than via the oral or parenteral route. Rarely does the condition develop after radiation therapy [56]. Risk factors include prior atopy or asthma, a history of allergic reaction to other or related drugs, and repeated courses of treatment with the drug which sensitize patients [18]. Typical signs and symptoms include dyspnea, a dry cough, fever, chest pain or discomfort, a skin rash and, rarely, heart involvement. Systemic involvement can be present in patients with elevated blood eosinophils, and this suggests the drug-induced Churg-Strauss syndrome. Hypoxemia correlates with the extent of pulmonary opacities, and symptoms are more prominent if an eosinophilic bronchitis is present, and this is suspected if wheezing is audible. An eosinophilic pleural effusion has been described in a few patients. The pattern of apical peripheral subpleural opacities on imaging (the 'photographic negative of pulmonary edema') certainly is distinctive; however, it is found in less than half the cases with eosinophilic pneumonia. The opacities can be localized, diffuse or migratory, or may appear as faint shadowing or a discrete diffuse ground-glass pattern. Kerley B lines have been described in drug-induced PIE. Thus, it may be difficult to distinguish PIE from cellular interstitial pneumonia or from cardiac interstitial edema on chest films. On HRCT, the opacities of PIE range in density from a discrete haze to patchy subpleural crescentic shadowing or diffuse consolidation. Mediastinal lymph node enlargement is an occasional finding. PIE is diagnosed by the presence of increased numbers of eosinophils in the blood (which can be as high as 80%), BAL or lung tissue. Sometimes, peripheral and/or BAL eosinophilia is lacking, and the diagnosis is made on histology. Eosinophilia is suppressed if corticosteroids are given. IgE levels may be increased in serum. BAL commonly shows an increase in eosinophils or both eosinophils and lymphocytes [14, 18]. On histology, there is an interstitial infiltrate of eosinophils admixed with mononuclear cells. Eosinophils may cluster around arterioles, without, however, invading their walls. An active vasculitis raises suspicion of the Churg-Strauss syndrome. Inconspicuous areas of OP may be present, and some patients may present with overlapping features of eosinophilic pneumonia and OP, and separating the two conditions may be problematic. However, the management of both conditions when they are related to drugs is similar, with drug withdrawal and, if required, corticosteroid therapy. Relating PIE to drug exposure is straightforward if definite blood or BAL eosinophilia is present, if patients are exposed to one eligible drug and if drug withdrawal is followed by improvement of symptoms on imaging. Drug withdrawal may not translate into measurable improvement in patients with extensive involvement, thus requiring corticosteroid therapy which, generally, quickly reverses all manifestations of PIE. Mild subclinical blood eosinophilia may persist for a few weeks or months after drug withdrawal with, seemingly, no adverse long-term consequences. Rechallenge with the causative medicine leads to recurrence of symptoms, blood and BAL eosinophilia, and pulmonary infiltrates. Rechallenge apparently carries little risk, as constitutional symptoms and increased blood eosinophilia act as early warning signs of relapse. However, caution is required, inasmuch as the diagnostic contribution of rechallenge is questionable if drug dechallenge was followed by improvement, or if an alternate drug is available to treat the basic disease. In previous studies, some patients who developed PIE as a result of exposure to the bowel disease-modifying drugs sulfasalazine and mesalazine were rechallenged with incremental doses of the drug, achieving desensitization, resumption of treatment with a full dose of the drug and maintained control of the background bowel disease [57, 58].

✻ APT (Amiodarone Pneumonitis) (fig. 6a, b)

Amiodarone is an antiarrhythmic agent with an imposing adverse effect profile. APT was recognized in 1980 in the US, possibly because higher dosages of the drug were

used to control ventricular arrhythmias in that country compared to Europe. Amiodarone and its metabolite desethylamiodarone accumulate in many organs, achieving concentrations in lung tissue that are toxic to lung cells. Two iodines are present for each molecule of amiodarone or desethylamiodarone. During chronic treatment with amiodarone, both amiodarone and the metabolite accumulate in the lung and interfere with the normal processing of endogenous phospholipids, which also accumulate in lung. Amiodarone and its metabolite have a very long tissue half-life, and will efflux very slowly (i.e. within 6–12 months) upon drug withdrawal. These peculiar pharmacokinetic features account for the distinctive profile of APT, with its slow onset, sluggish improvement after drug discontinuance, possible development after termination of treatment with the drug, relapses after drug withdrawal, high CT numbers on HRCT and evidence of dyslipidosis on histology. The beneficial effect of corticosteroid therapy in the vast majority of patients suggests that inflammation is present in addition to metabolic disturbances. APT may evolve to produce pulmonary fibrosis [17].

The incidence of amiodarone pneumonitis is between 0.1 and 50% in patients on low or high dosages of the drug, respectively. Low-dosage regimens have brought the incidence of pulmonary infiltrates thought to represent APT from 5–15% above background in patients on ≥ 500 mg of amiodarone daily, down to 0.1–1.6% in those treated with ≤ 200 mg [59]. Onset of APT is unpredictable and insidious, and may occur after a few weeks or up to several years into treatment. On average, APT develops 18–24 months into treatment. A subclinical increase in the erythrocyte sedimentation rate may precede the clinical onset of APT. The disease is usually diagnosed approximately 2 months after the onset of clinical symptoms, which leaves room for earlier diagnosis. Early onset of APT a few days after initiation of treatment with the drug is unusual, and may indicate a history of a recent loading dose of amiodarone. An acute onset of APT over a few days is also unusual, and suggests amiodarone-induced inflammation superimposed on a background of metabolic disturbances. Clinically, APT manifests with dyspnea, a dry cough, weight loss, malaise, moderate fever and, sometimes, mild pleuritic chest pain. Crackles and moist rales are a common finding at auscultation. A friction rub is present in a few patients. Leukocytosis and an increase in circulating lactate dehydrogenase levels are common features, and the latter can precede the clinical onset of the disease. The role of serum brain natriuretic peptide levels in distinguishing APT from interstitial or alveolar cardiac pulmonary edema is imprecise, inasmuch as patients may present with an association of both conditions [54]. Adverse effects of amiodarone in the liver or thyroid are occasionally present in association with the pulmonary toxicity, and appropriate tests are required to detect these complications. A hyperthyroid state may increase the perception of dyspnea in APT.

APT is a disease of the alveolar and interstitial compartments. Thus, APT is characterized by alveolar, interstitial or mixed opacities on imaging [34, 60–63]. The impression is that patients with APT all have distinct patterns of involvement on imaging, and it is easy to be misled. Radiographic appearances include bilateral, often asymmetric interstitial or alveolar infiltrates, which may involve all areas of the lung fields bilaterally, including the apices. A moderate loss of volume is generally present, and dominates on the side of greater involvement. The opacities of APT may assume a recognizable lobar distribution, and there is an impression that the right lung (mainly the right upper lobe) is more frequently or more densely involved than the left. Opacity and volume loss of the right upper lobe is suggestive. Patients may present with apparently unilateral involvement, but contralateral opacities are generally visible on CT. Other patterns include a lone mass or multiple masses abutting the pleura, which can be thickened. These masses can simulate pulmonary infarction, infectious pneumonia or OP, peripheral lung carcinoma or pulmonary lymphoma. APT sometimes presents in the form of multiple shaggy nodules, which may be surrounded by a halo corresponding to attenuated amiodarone pneumonitis peripherally [64]. Rarely, the disease manifests with large biapical nodules with a center of decreased attenuation on CT. On HRCT, the involvement is often patchy and asymmetric, with areas of haze, ground-glass pattern, intralobular linear opacities, alveolar shadowing or dense consolidation, or masses with high attenuation numbers. Pleural thickening is a common finding en face the areas of parenchymal involvement. Even though the chest radiograph indicates unilateral disease, HRCT often indicates bilateral disease with minor contralateral opacities. In a study of 20 patients with mild reversible APT [62], all patients had ground-glass opacities, while areas of consolidation were found in 4 and intralobular reticulations in 5. A subpleural distribution of the opacities was more common than a central distribution (in 18 vs. 2 patients). High density in the area of APT was present in 8 of the 20 patients. In advanced disease, increased attenuation seems a consistent feature of APT [60]. An exudative pleural effusion is occasionally present in association with parenchymal

disease [53]. APT may produce attenuated changes on imaging in patients with COPD or emphysema. A few patients on amiodarone present with subclinical pulmonary infiltrates, and careful follow-up is required to determine whether these are drug related.

Interpretation of PFTs in APT is made against a background of COPD or restrictive lung dysfunction from chronic left ventricular failure, two conditions commonly present in patients receiving amiodarone [54]. Restrictive lung dysfunction, decreased diffusing capacity and arterial hypoxemia are generally present in APT, and these are more severe in patients with extensive disease. Hypoxemia is more severe in patients with a background of COPD or emphysema.

The contribution of BAL to the diagnosis of APT is controversial, because a wide range of cellular abnormalities can be found [14, 65]. These include an increase in neutrophils and/or lymphocytes, or even a normal distribution. Eosinophilia as an isolated finding in BAL is rare. BAL lymphocytosis suggests inflammation, and tends to be associated with a shorter time to onset of the pneumonitis. Foam cells containing lamellar inclusions on microscopic or electron microscopic examination indicate chronic exposure to amiodarone, and this is a routine finding which does not necessarily indicate toxicity [66]. However, the absence of foam cells is against the diagnosis of classic (i.e. not acute or atypical) APT. Hemosiderin-laden macrophages or alveolar hemorrhage have been described in the BAL in a few patients.

APT often remains a diagnosis of exclusion, because lung biopsy is now rarely performed, as patients often deteriorate after the procedure, and the risk may outweigh the benefit [54]. A lung biopsy is meaningful, however, in patients with ventricular arrhythmia in whom pulmonary infiltrates develop and there is no substitute for amiodarone, or in those in whom valve surgery or heart transplantation is contemplated and the diagnosis of pulmonary infiltrates must be established. In most other patients, it is reasonable to narrow down the diagnostic possibilities by noninvasive or indirect tests such as BAL and cardiac evaluation, and to proceed with drug withdrawal, corticosteroid therapy and careful follow-up. The histopathological appearances of APT include septal thickening by interstitial edema, nonspecific inflammation, interstitial fibrosis and the presence of lipids within interstitial, endothelial and alveolar cells, and lying free in the alveolar lumen [35, 67]. A large number of free foamy macrophages support the diagnosis of APT, and these cells may be so numerous as to mimic desquamative interstitial pneumonia. Other findings include OP, or fibrinous pneumonia *and* OP, type II cell hyperplasia, and diffuse bland interstitial fibrosis. Active or resolving DAD and hyaline membranes characterize those cases with acute severe APT or ARDS.

There is general agreement that corticosteroids positively influence the outcome of APT. These drugs are indicated in most cases because drug withdrawal is often not followed by convincing improvement, and nonresolving APT may rapidly evolve toward irreversible pulmonary fibrosis. If indicated, corticosteroids should be given for several months, and tapered prudently, otherwise APT may recur owing to the persistence of amiodarone in the lung. A relapse of APT following too rapid steroid tapering may prove much more difficult to control than the first episode of APT. Overall, the mortality in APT is less than 10% in ambulatory patients, but it is higher (20–33%) in patients who are diagnosed late or who require admission to the hospital for this condition.

There is no current consensus on when and how often chest radiographs and pulmonary function should be measured in patients receiving long-term amiodarone [17, 59], and practices vary widely [68]. Chest radiographs should be taken prior to the commencement of treatment with amiodarone and at regular intervals thereafter (e.g. every 4–12 months), depending mainly on drug dosage. Two to three baseline PFTs at the commencement of treatment with amiodarone and shortly thereafter will serve as a reference to which further changes can be compared. Routine follow-up of PFT is unrewarding, as APT can develop rapidly between two sets of measurements, and radiographic abnormalities may not precede clinical toxicity. Pulmonary function and the diffusing capacity should be reevaluated, if otherwise unexplained symptoms or new pulmonary infiltrates develop on imaging. The earliest functional abnormality in APT is a precipitous and consistent decrease in the diffusing capacity of carbon monoxide. Left ventricular failure and pulmonary edema alter this measurement to a lesser extent than does APT. An isolated decrease of the diffusing capacity does not necessarily indicate clinically recognizable disease, as overt APT will develop only in a third of such patients. This is why PFT should be performed only if imaging abnormalities are present or develop. An isolated reduction of the diffusing capacity should not prompt discontinuation of amiodarone (because this carries an intrinsic risk of recurrence of the arrhythmia), unless there is clinical or imaging evidence of APT. In this situation, repeated measurements of this parameter over a shorter period of time are indicated. A stable diffusing capacity with time indicates the lack of clinically meaningful APT.

Self-reporting of symptoms, serial clinical evaluation and chest radiographs are indicated in patients on long-term amiodarone. These are probably the easiest and most useful strategies for the prompt detection of APT.

* OP or Bronchiolitis Obliterans OP (BOOP)

OP has many causes other than drugs, making evaluation of drug causality difficult [69]. The condition is characterized by alveolar and ductal fibrosis as the dominant histopathological feature. Early cases of drug-induced OP were reported during treatment with the early antihypertensive drugs hexamethonium and mecamylamine [1]. Then, nodular OP simulating pulmonary metastases on HRCT was described during treatment with bleomycin in young persons [70]. Eventually, amiodarone, β-blocking agents, carbamazepine, ergolines, gold, interferons, methotrexate, minocycline, nitrofurantoin, penicillamine, sulindac and radiation therapy to the breast were all recognized to produce an OP pattern [69]. Circumstantial evidence relates OP to treatment with ACEIs, NSAIDs, inhibitors of 3-hydroxy-3-methyl glutaryl-coenzyme-A reductase (statins) and a few other drugs [1]. Clinically, drug-induced OP manifests with dyspnea, low-grade fever and, sometimes, lancinating or acute pleuritic chest pain.

Several clinical imaging patterns are recognized. Typically, the disease is suspected when migratory opacities are seen on chest films taken sequentially over a few weeks or months [69, 71]. There may be intervening periods with a normal chest radiograph despite continued exposure to the drug. The opacities generally disappear after simple drug withdrawal, and there is no relapse if the patient is not rechallenged. In other cases, the opacities are in the form of a lone mass or masses, or may have a recognizable segmental or lobar distribution. These may not respond to drug discontinuance. Patchy or stellate shadows along the bronchovascular bundles suggest OP related to chronic treatment with nitrofurantoin [3, 72]. Other patterns include multiple shaggy nodules (with the use of bleomycin, carbamazepine, minocycline or statins), biapical masses with the use of mesalazine or sulfasalazine in inflammatory bowel disease [58], and diffuse pulmonary infiltrates with the use of nitrofurantoin or penicillamine [45].

No distinctive BAL pattern has been described in association with drug-induced OP. Often, however, lymphocytes and sometimes neutrophils and/or eosinophils are increased in the BAL. If a lung biopsy is deemed necessary to reliably establish the diagnosis, the video-assisted approach is preferred to the transbronchial route, as areas of OP can be an incidental finding on a small biopsy specimen. Histology reveals interstitial inflammation, superimposed on the dominant background of alveolar and ductal fibrosis. In patients with amiodarone-induced OP, changes suggestive of APT can be present in association with OP. In a fraction of patients with OP, tissue eosinophilia is present as an associated feature, making the differentiation of OP from eosinophilic pneumonia difficult. Acute fibrinous OP shares some features with classic OP (including exposure to drugs) [73], but this condition has a more severe course than classic OP. On histology in acute fibrinous OP, there is a dominant pattern of intra-alveolar fibrin and OP associated with varying amounts of type II cell hyperplasia and interstitial edema, on a background of acute or chronic inflammation [73].

Distinguishing OP due to drugs from that due to a background disease can be problematic, as the condition has been described in association with multiple connective tissue diseases, polymyalgia rheumatica, inflammatory bowel disease and other conditions [43, 58]. In addition, except in amiodarone-induced OP where dyslipidosis can be present, the histopathology of OP is similar, regardless of which drug is causing this condition. In patients with moderate symptoms, drug discontinuance is justified and follow-up will indicate whether signs and symptoms of OP abate, supporting the drug etiology. Patients with OP improve with corticosteroid therapy regardless of the cause of the disease, and this cannot be used as a diagnostic test for a drug-induced condition.

Not all patients with migratory pulmonary opacities and a background of compatible exposure to drugs actually have OP, as the same imaging pattern can be seen in patients with drug-induced PIE [56, 74], and BAL may not separate the two conditions well. In patients with migrating opacities and mild symptoms, lung biopsy may not be justified, and the patient may be observed after drug withdrawal, which serves as a diagnostic test. Disappearance of symptoms and pulmonary opacities will support the drug etiology, even though the histopathologic background remains unclear. Should drug discontinuance not be followed by improvement within a few weeks, then a lung biopsy or a trial of corticosteroids is considered.

When the drug condition is not recognized, multiple relapses of OP can occur, even though corticosteroid drugs are still given at an elevated dosage, requiring repeated courses or an augmented dosage of corticosteroids. The OP associated with amiodarone may relapse during steroid tapering, even if the drug has been withdrawn several weeks or months earlier. Prolonged use, augmented dosage or reinstatement of corticosteroid therapy is indicated.

✻ Drug-induced pulmonary fibrosis (fig. 7) is mainly a complication of treatment with chemotherapeutic agents (particularly cyclophosphamide, BCNU and CCNU), amiodarone and, rarely, gold, sulfasalazine or methotrexate [1]. Due to the confounding influence of idiopathic pulmonary fibrosis, ascribing pulmonary fibrosis to drugs is often difficult, unless there is a definite temporal association between exposure to the drug and onset of the disease. Drug-induced pulmonary fibrosis can develop during or (up to many years) after termination of treatment with chemotherapeutic drugs [5, 75]. Drug-induced pulmonary fibrosis manifests with predominantly basilar streaky opacities and regional volume loss. Honeycombing and clubbing are late features. On HRCT, coarse interstitial reticular and perilobular opacities and traction bronchiectasis predominate in the lung bases.

Amiodarone-induced fibrosis can develop after an episode of nonresolving classic APT, especially if corticosteroids are not given or given late, or as a de novo phenomenon [17]. Criteria for the diagnosis of amiodarone-induced fibrosis include a normal chest radiograph prior to institution of treatment with amiodarone, development of fibrosis during or shortly after termination of treatment with amiodarone, the absence of other causes and, sometimes, the presence of prior APT with incomplete resolution. The histopathological features of amiodarone-induced fibrosis are those of severe interstitial fibrosis with thickened alveolar septa and type II cell dysplasia and honeycombing as late changes. Features suggestive of APT may be present in amiodarone-induced fibrosis, depending on the time from biopsy to discontinuation of the drug. Amiodarone-induced fibrosis may have a more rapid progression with time as compared to idiopathic pulmonary fibrosis. The prognosis of amiodarone-induced fibrosis is poor, but some patients may stabilize on steroids.

A peculiar pattern of pleuropulmonary fibrosis can be observed in adults after the administration of carmustine, cyclophosphamide or multiagent chemotherapy in childhood [75, 76]. The features are a pattern of upper-lobe fibrosis, which involves the upper and lateral aspects of the lung and, sometimes, the pleura laterally in a manner mimicking late radiation injury. In children, there is also progressive anteroposterior narrowing of the chest, which contributes to the restrictive physiology later in life. Clinically, there is dyspnea and, sometimes, marked chest pain and a friction rub. Although not many cases are available for review, the outcome of this condition is grim, with lack of response to corticosteroids and a 50% mortality.

Patients with drug-induced fibrosis, especially if produced by chemotherapeutic drugs, may suffer repeated episodes of pneumothorax which are difficult to treat, as the fibrotic lung reexpands poorly.

Pulmonary infiltrates or subpleural foci of rounded atelectasis (folded lung) can develop in association with pleural fibrosis due to prolonged exposure to ergot drugs [1, 77]. Although the disease is referred to as drug-induced 'pleuropneumonitis', parenchymal changes may be nonspecific changes secondary to pleural involvement.

Drug withdrawal is indicated in all cases with drug-induced fibrosis. However, this is rarely followed by improvement. The response to corticosteroid drugs is often limited. Lung transplantation is an option in a few patients. It is tragic when a patient with a cured malignancy dies from therapy-related pulmonary fibrosis.

Exogenous lipoid pneumonia is a complication of chronic aspiration of mineral oil (paraffin) [78]. Classically, contamination with the oil occurs during long-term administration of paraffin to combat constipation. Patients with aspiration or achalasia and elderly patients are at risk. Less commonly, exogenous lipoid pneumonia results from inhalation or aspiration of amphotericin B or cyclosporin dissolved in lipid, from intranasal application of mineral oil or from compulsive use of lipsticks. Rarely, application of oil-containing gauze on chest wounds, prolonged use of oil-containing eyedrops and smoking of cigarettes coated with cannabis oil produce the condition. Spreading and/or aspiration of the nondigestible oil leads to alveolar filling and an interstitial reaction, and later to the development of pulmonary fibrosis. Lipoid pneumonia manifests as predominantly basilar or diffuse opacities [79–81], or in the form of a solitary round-shaped mass called paraffinoma, or multiple irregular masses. On HRCT, alveolar filling creates a ground-glass pattern, and a crazy-paving pattern has been reported. The opacities have low attenuation numbers, and often remain at some distance from the pleural surface. Pulmonary vessels may be visible within the areas of greater parenchymal involvement on contrast nonenhanced CT, a sign referred to as the 'spontaneous angiogram'. The BAL commonly has a milky or oily appearance. A lymphocytic or neutrophilic alveolitis can be present as an associated feature. Ideally, the diagnosis of lipoid pneumonia is suggested at history taking, and is confirmed by the finding of lipids in BAL fluid or in vacuoles in cells retrieved in sputum or BAL. Mineral oil stains positive with oil red O and Sudan black, and the BAL fluid or lung tissue can be submitted to chromatography or mass spectrometry to confirm the presence of exogenous lipids. A lung biopsy is rarely

required for diagnosis. However, exogenous lipoid is often missed at history taking, and about 50% of patients in one series were diagnosed in retrospect after the lung biopsy showed suggestive changes. The histopathologic appearance and staining pattern enable the distinction of exogenous lipoid pneumonia from amiodarone pneumonitis and from a naturally occurring lipid storage disease. Patients may not improve after withdrawal of lipid-containing products. Corticosteroid therapy is associated with modest benefit, if any. The outcome is difficult to predict, and seems poorer in the elderly, with recurrent bouts of bronchopneumonia or superinfection with atypical mycobacteria or *Aspergillus* spp., or the development of severe pulmonary fibrosis or lung carcinoma.

✻ Drug-Induced Granulomatosis and Sarcoidosis

Granulomas, not the clinical entity of sarcoidosis, are an occasional finding in lung or lymph node biopsies of patients exposed to etanercept, methotrexate, phenylbutazone, phenytoin, sirolimus and chemotherapy regimens containing bleomycin [1].

The pulmonary reaction associated with intracavitary BCG therapy is distinctive [33, 82, 83]. The condition is characterized by diffuse granulomas in the lung, which can produce acute respiratory distress. Granulomas can also be found in the liver or be diffuse. In patients with severe symptoms, it is important to separate BCG-induced granulomas from BCG infection. Appropriate staining and molecular techniques in BAL and lung tissue are required to separate these entities. Treatment consists of corticosteroids and corticosteroids *plus* antituberculous agents in BCG granulomatosis and infection, respectively [84].

Drug-induced sarcoidosis, not just granulomas, is associated with the use of interferon-α and -β in the treatment of hepatitis C infection, multiple sclerosis, hematologic malignancies and solid tumors [85]. The pegylated form of interferon can also produce sarcoidosis. Sarcoidosis rarely develops after withdrawal of the drug. The condition develops after a few months into treatment. Interferon can also produce reactivation of earlier naturally occurring sarcoidosis. Clinically, patients present with malaise, breathlessness and cough. These manifestations can mimic the flu-like symptoms that usually accompany the first weeks of treatment with interferon. Interferon-induced sarcoidosis reproduces the clinical, imaging and histopathologic picture of naturally occurring sarcoidosis, with involvement of mediastinal lymph nodes, lung (with BAL lymphocytosis), skin (including erythema nodosum and Löfgren syndrome), liver, central nervous system, kidney and calcium homeostasis. Noncaseating granulomas can be found in lung, bronchial mucosa, mediastinal lymph nodes, skin and internal organs. Interferon-induced sarcoidosis is improved in a few months with reduction in drug dosage, drug withdrawal or corticosteroid therapy. In some patients, the condition fails to improve or may progress despite drug discontinuation, and corticosteroid therapy is required. No patient has yet progressed to the late stage of pulmonary fibrosis seen in naturally occurring sarcoidosis.

ILD Associated with Drug-Induced Vasculitis

Leukotriene receptor antagonists are used as corticosteroid-sparing agents in asthma. Recently, leukotriene receptor antagonists were associated with the development of the Churg-Strauss syndrome [86–89]. Although there are several convincing case histories, a reporting bias cannot be excluded, as recent studies indicate that overall, the incidence of Churg-Strauss syndrome has not changed in the recent past [90]. The condition manifests with blood eosinophilia, pulmonary infiltrates and extrapulmonary involvement including cardiomyopathy, muscle pain, mononeuritis and, sometimes, digestive or dermatological involvement. Onset of the disease occurs a few weeks or months into treatment with the drug. Churg-Strauss syndrome associated with leukotriene receptor antagonists in asthma may follow corticosteroid tapering or withdrawal. Although the pathologic features of naturally occurring Churg-Strauss syndrome include a combination of eosinophilic pneumonia, granulomatous inflammation and vasculitis, no specific description of the drug-induced condition is available.

Circumstantial evidence relates treatment with macrolides, aspirin, hepatitis B vaccination and immunotherapy to the development of Churg-Strauss syndrome [1].

The possibility that drugs may induce Wegener's granulomatosis remains speculative at this time [42].

Drug-induced veno-occlusive disease is a rare complication of drug and radiation therapy [91–93]. The condition refers to diffuse obliteration of pulmonary venules by fibrous tissue. This entity has also been reported in oncology patients after treatment with bleomycin, carmustine, gemcitabine, mitomycin, vinca alkaloids and radiotherapy. However, veno-occlusive disease has been reported in the context of solid or hematologic malignancies, prior to any form of treatment. Patients present with dyspnea, ill-defined interstitial opacities and Kerley B lines. Postcapillary pulmonary hypertension and right heart failure eventually develop. The contribution of drugs or radiation therapy versus the underlying malignancy or a

chance association needs to be evaluated on a case-by-case basis.

Endogenous fat embolism and pulmonary infiltrates can develop shortly after liposuction. Symptoms include dyspnea, chest pain and transient pulmonary infiltrates. The disease is often self-limited [94].

Total parenteral nutrition [95] and propofol [96] can cause exogenous fat embolism with deterioration of gas exchange and changes in the cellular and lipid profile in the BAL.

ILD in Drug-Induced Systemic Conditions

In addition to the DAH syndrome, which may indicate drug-induced vasculitis (see above) [21], pulmonary infiltrates, rarely an ARDS picture, can occur in the following conditions:

- The hemolytic and uremic syndrome can develop in the form of renal failure, anemia, hemolysis, schizocytosis and pulmonary hypertension during or within months after treatment with mitomycin C or gemcitabine [97, 98].
- The drug hypersensitivity syndrome (DHS) [99], which is also called 'drug rash with eosinophilia and systemic symptoms', the anticonvulsant, carbamazepine or sulfone (hypersensitivity) syndrome. DHS is an idiosyncratic reaction defined by the clinical triad of fever, rash and internal organ involvement such as hepatitis, myocarditis, nephritis or pulmonary infiltrates. The disease develops within the first few weeks into treatment with anticonvulsants, with an attack rate of 1 out of 5,000–10,000 patients. DHS is also described with the use of allopurinol, other aromatic anticonvulsants and sulfonamides. Less common inducers of the syndrome include abacavir, atenolol, azathioprine, bupropion, captopril, diltiazem, gold salts, leflunomide, minocycline, nevirapine, oxicam NSAIDs, sulfasalazine and trimethoprim. Onset is often gradual, with fever and papulopustular erythematous skin reactions as the first indicators. The presentations of DHS include dermatological, hematologic (anemia, thrombopenia, leukemic reactions), lymphatic or internal organ involvement, which can mimic systemic diseases or an infection. The severity or extent of the skin-related changes do not correlate with the severity or extent of internal organ involvement, which may remain asymptomatic or be life-threatening. Eosinophilia and atypical lymphocytosis occur in up to 30% of cases. Thoracic manifestations of DHS occur in about 10% of patients, and include lymphoid interstitial pneumonia, NSIP, eosinophilic pneumonia, OP, pleural effusion and lymph node enlargement, which may progress to frank lymphoma or Hodgkin's disease. Treatment consists of withdrawal of all suspect drugs, followed by supportive care of symptoms and corticosteroid therapy. The mortality rate is 8–10%. Patients must avoid reexposure to the causative medication and to any related aromatic compounds (phenytoin, carbamazepine, phenobarbitone). Because genetic factors are suspected in DHS, relatives should be instructed as regards their enhanced risk of developing similar reactions, should they take similar medications [12, 100–103].
- Although the pleura is involved more frequently than the lung in drug-induced systemic lupus erythematosus (DI-SLE), pulmonary infiltrates sometimes develop in this condition [12]. Drug-induced lupus has been reported with about 60 unrelated drugs, including amiodarone, ACEIs, anticonvulsants (carbamazepine, ethosuximide, phenytoin, primidone, trimethadione and valproate, but not benzodiazepines or phenobarbital), anti-TNF agents, β-blockers (mainly acebutolol), chlorpromazine, oral contraceptives, recombinant cytokines or antibodies, dihydralazine, interferons, mesalazine, methyldopa, minocycline, nitrofurantoin, propylthiouracil, statins, sulfasalazine and ticlopidine [1]. It is estimated that drugs cause approximately 15–30% of all cases of lupus. Drug-induced lupus is clinically and biologically different from naturally occurring lupus. The former condition is often diagnosed late, after long periods of disabling symptoms. Diagnostic criteria include the conjunction of treatment with an SLE-inducing drug, positive ANA without, generally, the presence of anti-double-strand DNA antibodies and a suggestive clinical picture. The prevalence of pleuropulmonary manifestations in DI-SLE is between 15 and 60%, depending on the causative drug [104]. Common manifestations of drug-induced lupus include chest pain, cough, dyspnea, arthralgias, skin changes, fever, malaise, pleuritis and pleural or pericardial effusion. Pulmonary infiltrates occur in isolation (i.e. without pleural manifestations of the disease) in a small minority of patients. For instance, mild pulmonary infiltrates were described in one case of DI-SLE induced by lovastatin. In another case with fluvastatin-induced lupus, DAD and an ARDS picture developed [1]. The lupus anticoagulant and antiphospholipid antibodies are present in a few patients, and may produce thromboembolic phenomena or a hypercoagulable state. Alveolar hemorrhage is not a feature of DI-SLE, contrasting to naturally occurring lupus erythematosus. Management of DI-SLE consists of drug withdrawal, and therapy with corticosteroids, immunosuppressives or plasma exchange is reserved for severe reactions. Clinical manifestations reverse more quickly than do the levels of

ANA, which may persist for months and slowly decrease with time.

ILD Resulting from Radiation Therapy to the Chest

Irradiation has long been known to cause dose-related, generally reversible changes in the lung [9]. These are characterized by a dry cough and the pathologic changes of bizarre type II cells, hyaline membranes, edema and eventually fibrosis. Similar pathologic changes can be produced by alkylating agents. Radiation lung injury can develop during or following radiation therapy for carcinoma of the lung or breast, Hodgkin's disease or non-Hodgkin's lymphomas, or after total body irradiation in candidates for bone marrow or peripheral stem cell transplantation. The expression of radiation injury to the lung depends upon the nature of the ionizing radiation, and the dose and direction of the radiation beam. The pattern of radiation pneumonia has changed with time, as radiation and delivery techniques have improved. Radiation therapy for lung cancer tends to produce localized unilateral changes, while mantle-field irradiation for Hodgkin's disease or lymphoma can produce changes in the upper chest, mediastinum and supraclavicular areas.

Three lines of evidence suggest that radiation therapy can produce changes in areas of the lung that are remote from the radiation beam. BAL lymphocytes are increased, and radioactive gallium is taken up in the nonirradiated as well as in the irradiated lung. In a few patients, radiation injury spreads out from the irradiated lung field to involve the lung diffusely in the form of acute radiation pneumonitis with, sometimes, an ARDS picture [9]. Lastly, OP or eosinophilic pneumonia has been shown to develop in nonirradiated areas of the lung following breast radiation therapy. In contrast to drugs, radiation therapy can also involve the pleura, heart, pulmonary veins, mediastinum, lymphatic vessels and nerves, creating manifold possibilities of thoracic involvement. The risk of radiation pneumonitis depends on the dose delivered to the lung, the fractionation schedule, a history of remote or current treatment with the chemotherapeutic agents oxygen or interferon-gamma, and individual factors. Other risk factors include older age and low baseline pulmonary function or PaO_2. Current smoking may have a protective effect. Recent pulmonary ablative surgery is also a risk factor, as pulmonary reserve is compromised, and more remaining lung can be exposed to radiation as postpneumonectomy hemithorax contracts.

Classic radiation pneumonitis is also called sporadic radiation pneumonia [9]. This is a common form of radiation-induced damage, with approximately 10% of patients who receive radiation therapy to the chest developing some radiographic changes consistent with radiation pneumonitis. When present, symptoms include a dry cough, moderate fever and dyspnea. On imaging, changes develop 1–2 months after the beginning of treatment, in the form of a discrete haze, ill-defined patchy nodules or an area of condensation with volume loss. The changes predominate in the irradiated area, and may reverse within 6 months, or progress towards an area of fibrosis which, with time, becomes sharply demarcated along the radiation beam, and may exhibit traction bronchiectasis. Mildly restrictive lung function develops early in the course of sporadic radiation pneumonitis, and the lung volumes generally normalize in 18–24 months. A lung biopsy is very rarely needed to establish the diagnosis of radiation pneumonitis. The histological features include interstitial edema, hemorrhage and a fibrinous exudate in the early stage of the disease with, later, distortion, fibrosis and type 2 cell dysplasia. Symptomatic patients with sporadic radiation pneumonitis respond well to the administration of corticosteroids. However, these drugs are not required in all cases, and treatment is guided by the severity of symptoms and the presence of hypoxemia. Late complications of chronic radiation pneumonitis include bronchiectasis in the fibrotic area, pneumothorax and colonization by *Aspergillus* spp. Late radiation-induced myocardial or valvular injury can be associated with chronic radiation pneumonitis, and may produce pulmonary infiltrates related to pulmonary congestion. With the current use of three-dimensional radiation portals, infiltrates from radiation therapy may not result in the traditional straight-edged infiltrate and may be more difficult to distinguish from other entities.

Rapid extension of the infiltrates shortly after radiation therapy to the chest or in candidates for bone marrow graft who have received conditioning chemotherapy and total body irradiation suggests the diagnosis of acute radiation pneumonia [105]. In addition to radiation dose and port size, recent administration of chemotherapeutic drugs or oxygen, or rapid corticosteroid withdrawal are risk factors. Acute radiation pneumonitis is associated with significant symptoms and, in some patients, develops into respiratory failure or an ARDS picture. Patients may respond satisfactorily to the administration of corticosteroids.

OP following radiation therapy to the breast is a recently recognized entity [106]. The disease is typically diagnosed when migratory opacities develop a few weeks to a few months after radiation therapy to the breast in the context of mild respiratory and constitutional symptoms.

Radiation-induced OP is attributed to priming of lung tissue by radiation, and is controlled by corticosteroids in a manner not dissimilar from OP of other causes.

Recently, chronic eosinophilic pneumonia was reported in female patients 1–10 months (average 3.5 months) after radiation therapy for breast cancer [56]. All patients had a history of asthma and/or atopy, a feature similar to the history in drug-induced eosinophilic pneumonias. Eosinophilia was present in blood or BAL in all cases. The radiographic appearances included pulmonary infiltrates in the irradiated lung in three women, and bilateral infiltrates in the remaining two patients. In one patient, the pulmonary opacities were shown to migrate from one area of the lung to another. Corticosteroid therapy was associated with prompt recovery, although symptoms recurred after corticosteroid withdrawal, as is the case in OP.

Microspheres containing therapeutic doses of ^{131}I or ^{90}Y are infused via the intravenous and hepatic arterial route to treat thyroid or hepatocellular carcinoma, respectively. Following spillage in the circulation, a sizable fraction of the microspheres may lodge in the pulmonary circulation, causing considerable irradiation and tissue damage. Transient or, more often, irreversible changes develop in 5–10% of patients after one or more treatment courses. Early disease is in the form of alveolar infiltrates and respiratory failure, or an ARDS picture. Later changes are in the form of distinctive symmetric opacities at a distance from both the pleura and the hilum [107, 108]. The prognosis of this condition is poor.

Acknowledgements

We wish to thank the secretarial office of the Department of Pulmonary and Intensive Care (University Medical Center Le Bocage and Medical School, Université de Bourgogne, Dijon, France) for literature searches, and Caroline Martin for excellent editorial assistance. We would also like to thank all physicians who contributed one or several cases of drug-induced lung disease. Further literature and specific queries are welcome on Pneumotox® [1] or at the above address.

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