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Cryptogenic organising pneumonia

J-F. Cordier

ABSTRACT: Organising pneumonia is defined histopathologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue. Although nonspecific, this histopathological pattern, together with characteristic clinical and imaging features, defines cryptogenic organising pneumonia when no cause or peculiar underlying context is found. Rapid clinical and imaging improvement is obtained with corticosteroid treatment, but relapses are common after stopping treatment.

KEYWORDS: Cryptogenic organising pneumonia

Although previous partial descriptions can be traced back to the latter half of the nineteenth century, as in the lectures given in 1877–1878 by J.M. Charcot in Paris, France [1], the concept of organising pneumonia (a term describing a histopathological pattern) emerged under various names at the beginning of the 20th century [2–9] (fig. 1). For example, MILNE [5] described a type of pneumonia ''where the usual process of resolution has failed and organisation of the inflammatory exudate in the air alveoli of the lung by fibrous tissue has resulted'' (resolution was the third stage in the course of pneumonia as described by Laennec, which followed the stages of congestion and hepatisation). These early observations were mostly made during the autopsy of patients who died due to nonresolving pneumococcal pneumonia before the era of antibiotherapy. These histopathological descriptions of organising pneumonia stated that the initial intra-alveolar material consisted of fibrin, further colonised by fibroblasts and replaced by ''fibrillated connective tissue'' [6]. Intra-alveolar buds of granulation tissue consisting of intermixed myofibroblasts, fibroblasts, and connective matrix, especially consisting of collagens are the hallmark of organising pneumonia.

Organising pneumonia has long been described in the context of pulmonary infection; for several decades, it was often considered as a nonsignificant histopathological witness of a precedent unrecognised infection. Nevertheless, sporadic studies indicated a continuing interest in this entity [10–14]. However, it eventually gained a more primordial status when it was correlated in the 1980s with specific clinico-radiological manifestations without any evident cause [15–19]. Cryptogenic organising pneumonia (COP), also called idiopathic bronchiolitis obliterans with organising pneumonia (BOOP) rapidly became, despite its relative rarity, a common disorder that was especially gratifying for the clinician due to its prompt improvement under corticosteroid treatment.

PATHOGENESIS

The most intriguing characteristic of intra-alveolar fibrosis, resulting from organisation of inflammatory exudates, is its usual dramatic reversibility with corticosteroids. Although the intra-alveolar buds in organising pneumonia share some morphological features with the fibroblastic foci present in usual interstitial pneumonia (UIP), in contrast to the latter they are not associated with progressive irreversible fibrosis. Therefore, intra-alveolar fibrosis of organising pneumonia represents a unique model of inflammatory lung disease [20, 21], offering many similarities with the process of cutaneous wound healing [22].

The morphological sequential evolution of intra-alveolar fibrosis in human organising pneumonia has been established previously [23–26] (fig. 2). Alveolar epithelial injury is the first event, with necrosis and sloughing of pneumocytes resulting in the denudation of the epithelial basal laminae. Most basal laminae are not destroyed, although

AFFILIATIONS
Service de Pneumologie, Center des Maladies Orphelines Pulmonaires, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Lyon, France.

CORRESPONDENCE
J-F. Cordier
Dept of Respiratory Medicine
Reference Centre for Orphan Pulmonary Diseases
Louis Pradel University Hospital
69677 Lyon (Bron)
France
Fax: 33 472357653
E-mail: jean-francois.cordier@chu-lyon.fr

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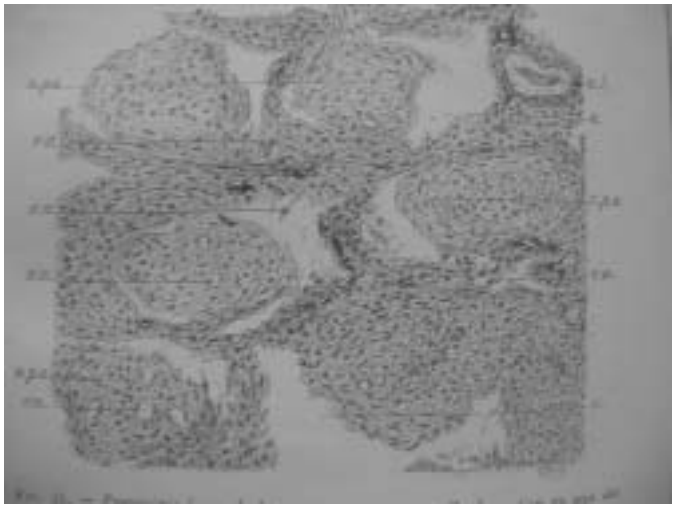

FIGURE 1. Historical figure showing intra-alveolar buds of granulation tissue with emphasis on neoformed vessels (en). Reproduced from TRIPIER [8].

some gaps are present. The endothelial cells are only mildly damaged. In contrast with diffuse alveolar damage, no hyaline membranes are found. Inflammatory cells (lymphocytes, neutrophils, some eosinophils) infiltrate the alveolar interstitium. Fibroblasts present in the interstitium exhibit features of activation, such as conspicuous rough endoplasmic reticulum and Golgi apparatus, but these are not increased in number and there are no associated collagen deposits.

The first intra-alveolar stage in the process of organisation is characterised by the formation of fibrinoid inflammatory cell clusters. These comprise prominent bands of fibrin together with inflammatory cells (especially lymphocytes, with some polymorphonuclears, and occasional plasma cells and mast cells). Macrophages engulfing fibrin may be seen.

The second stage is characterised by the formation of fibroinflammatory buds. Fibrin is fragmented and inflammatory cells are present but less numerous. Fibroblasts migrating from the interstitium through gaps in the basal laminae colonise the fibrin remnants and proliferate, as demonstrated by the presence of mitotic figures. Fibroblasts undergo further phenotypic modulation, especially with the development of intracellular filaments (myofibroblasts). A reticulin framework takes place in the extracellular environment. A proliferation of alveolar cells progressively provides re-epithelialisation of the basal laminae, a crucial phenomenon for the preservation of the structural integrity of the alveolar unit.

The third and final stage of the process of organisation is defined by the characteristic ''mature'' fibrotic buds. Inflammatory cells have almost completely disappeared in most buds (although some may persist in the centre of some buds), and there is no longer any fibrin within the alveolar lumen. Concentric rings of fibroblasts alternate with layers of connective tissue (mainly collagen bundles). The fibroblasts are typical myofibroblasts with conspicuous filaments in their cytoplasm oriented along the axis of the cells, with an abundant endoplasmic reticulum.

The matrix pattern of the intra-alveolar buds is initially characterised by fibrillar material consisting of fibronectin, type III collagen and proteoglycans, among which the typical periodic (type I) collagen fibres represent a minority, leaving large empty areas of the extracellular space. The cellular rings of fibroblasts–myofibroblasts are then intercalated with connective matrix sheets, consisting of loose bundles of thin collagen type I fibres mixed with fibronectin, collagen and procollagen type III and proteoglycans. In the mature fibrotic buds, the connective network consists of thin collagen I fibres held together by thinner fibrils of collagen and procollagen type III, and fibrin to form bundles resulting in a loose connective network where fibronectin, type III procollagen and collagen are codistributed at a higher rate than type I collagen. This contrasts with the predominant deposition of type I collagen in UIP. A loose connective matrix with high type III collagen content is more susceptible to degradation and reversal of fibrosis [24, 27, 28]. Glycoproteins, especially tenascin, are likely to play a role in loosening the adhesive interactions between cells and the pericellular matrix components in COP [29]. Collagen VI, coexpressed with collagen III rather than collagen I, may also participate in the regulation of matrix deposition in COP [30].

A further characteristic of the intra-alveolar buds in COP is the prominent capillarisation, which is reminiscent of granulation tissue in wound healing, another type of a reversible fibroinflammatory lesion [31]. Vascular endothelial growth factor and basic fibroblast growth factor are widely expressed in intra-alveolar buds [32]. Angiogenesis mediated by these growth factors could contribute to the reversal of buds in organising pneumonia.

Experimental models provide further information about the morphogenesis of intra-alveolar fibrosis. Paraquat in monkeys [33] or lobar instillation of $CdCl_2$ in rats [34] results in intra-alveolar migration of interstitial cells through gaps in the epithelial basement membranes after lung injury. The early damage to type I pneumocytes progressing to necrosis, leaving areas of denuded alveolar membrane with abnormal alveolar repair, is associated with failure of resolution in experimental streptococcal pneumonia in rats [35]. In intra-alveolar fibrosis produced by bleomycin in rats, alveolar structural remodelling is seen only when mural incorporation of intra-alveolar buds occurs [36].

An animal model of intraluminal fibrosis has been developed with intranasal inoculation of reovirus serotype 1 into CBA/J mice at a titre of 10^6 plaque-forming units (pfu) [37]. In this model, severe pneumonia, characterised by a prominent peribronchiolar lymphocytic inflammation, further evolves with the formation of intraluminal fibroblastic lesions indistinguishable from organising pneumonia. Interestingly, these lesions develop in CBA/J, but not in other strains of mice, suggesting that genetic host factors are critical in the development of intra-alveolar fibrosis. A model of diffuse alveolar damage with typical hyaline membranes and high mortality has been obtained with the same animal model but using a higher titre (10^7 pfu) of reovirus 1 [38, 39]. Thus, the degree of severity of the initial injury seems to be a critical determinant in the progression towards either organising pneumonia or diffuse alveolar damage [38]. Furthermore, whereas corticosteroids can both inhibit the development of fibrotic

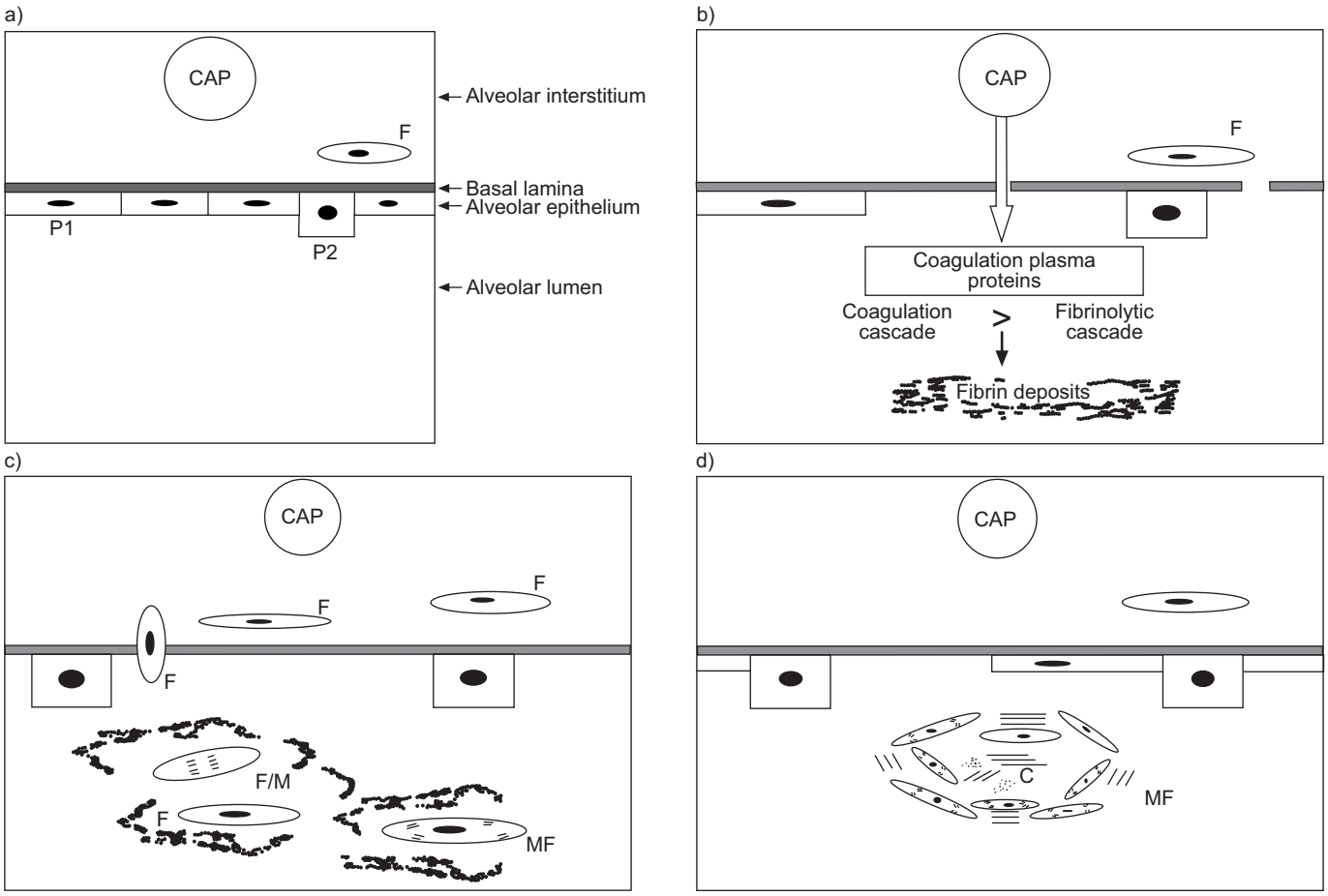

FIGURE 2. Mechanisms of intra-alveolar organisation. a) Normal alveolus. b) Epithelial alveolar injury with necrosis of pneumocytes (especially type I pneumocytes; P1), formation of gaps in the basal lamina, and intra-alveolar leakage of coagulation plasma proteins. The balance between coagulation and fibrinolytic cascades favours coagulation and results in intra-alveolar deposits of fibrin. c) Activation, proliferation and migration of the fibroblasts (F) within the alveolar lumen through gaps in the basal lamina. d) Most fibroblasts have acquired a phenotype of myofibroblasts (MF) and produce connective matrix proteins forming mature fibrotic intra-alveolar buds composed of concentric circular layers of MF and connective matrix. CAP: capillary; P2: type 2 pneumocyte; F/M: fibroblast undergoing mitosis; C: connective matrix (collagens, fibronectin, glycoproteins).

lesions and enhance the resolution of fibrotic lesions in the model of intraluminal fibrosis, in the diffuse alveolar damage model corticosteroids fail to modulate the development of the lesions at any stage [39]. The role of T-cells has been explored in the reovirus 1-induced lung injury model, with neonatal thymectomy in mice demonstrating that T-cells are required for the development of organising pneumonia, but not for that of diffuse alveolar damage [40].

The pathohistophysiology recognised by the previous morphological studies in human and animal models offers some cornerstones for the understanding of the biopathology of intra-alveolar fibrosis. The pathogenesis of pulmonary fibrosis involves a complex network and interaction of cells [41–43], mediators [44–48] and extracellular matrix (ECM) components [49–52].

Some other limited information has been published on biopathological features in organising pneumonia. Platelet-derived growth factor [53] and interleukin (IL)-8 [54] produced by macrophages are likely to play a role in the pathogenesis of intra-alveolar fibrosis in COP. Pulmonary tissue from rheumatoid arthritis patients with organising pneumonia contains many cells positive for S-100 protein [55]. B7-2 and class II major histocompatibility complex molecule expression in alveolar macrophages of patients with organising pneumonia is decreased compared with control subjects [56]. The soluble form of the Fas ligand (implicated in the system of apoptosis-signalling receptor molecules) is elevated in the bronchoalveolar lavage (BAL) fluid of patients with COP, which may abrogate the cytotoxicity of the Fas-ligand [57].

Mast cells and released tryptase are increased in the BAL fluid of patients with COP [58]. The cytokine profile of BAL in COP is characterised by increased monocyte chemotactic protein-1, IL-10, IL-12 and IL-18 levels with respect to controls and UIP, consistent with a marked degree of macrophage and lymphocyte activation with an expansion of T-helper type-1 response in COP [59].

Some insights into the pathogenesis of organising pneumonia may further be extrapolated with acceptable likelihood from studies in the other infiltrative and fibrosing lung diseases, especially acute respiratory distress syndrome (ARDS; which

is characterised by two successive stages of diffuse alveolar damage, namely acute exudative and chronic organising) [20, 21, 60, 61] and idiopathic pulmonary fibrosis (IPF) [62].

Clearly, epithelial alveolar damage with leakage of plasma proteins and further fibrin formation within the alveolar lumen is a crucial initial event, which has been especially studied in ARDS and further emphasised in pulmonary fibrosis [20, 21, 63–68]. The formation of fibrin results from an imbalance in the alveolar lumen between the coagulation and fibrinolytic cascades, with a net result of clotting [69]. Recently, increased levels of a potent inhibitor of fibrinolysis, thrombin activable fibrinolysis inhibitor, and of protein C inhibitor have been found in the BAL from patients with interstitial lung disease, especially COP [70]. In addition to providing a provisional fibrin matrix for the migration of cells (including fibroblasts), the coagulation and fibrinolysis factors and inhibitors (especially plasminogen activator inhibitor-1) play a complex role in fibrogenesis [68]. Interestingly, an animal model demonstrated prevention of bleomycin-induced lung fibrosis by aerosolisation of heparin or urokinase [71].

The matrix metalloproteinases (MMPs) that cleave protein components of the ECM play a central role in tissue remodelling [72]. Two collagenolytic metalloproteinases are involved in the destruction of subepithelial basement membranes, MMP-2 (preferentially secreted by fibroblasts and epithelial cells) and MMP-9 (preferentially produced by inflammatory cells). In organising pneumonia, MMP-2 is expressed in BAL fluid and by regenerated type II cells, in contrast with UIP where MMP-9 is preferentially expressed [73]. In another study, the concentration of MMP-9 and tissue inhibitors of metalloproteinases (TIMP) was increased more in the BAL fluid of patients with COP compared with UIP [74]. Although these studies are somewhat contradictory, they suggest that an imbalance between MMP and TIMP may play a role in the remodelling of connective tissue in COP. Interestingly, laminin-5 (a glycoprotein involved in cell attachment, migration, proliferation, differentiation and apoptosis), expressed in epithelial cells of wound healing, is also expressed in regenerating epithelial cells in COP, as well as in UIP [75]. However, re-epithelialisation is disturbed in UIP, which may contribute to the progression of fibrosis.

The role of the myofibroblast in wound healing and fibrosis is critical [76, 77]. The origin of fibroblasts–myofibroblasts involved in organising pneumonia is not known. Several recent papers have demonstrated that myofibroblasts involved in pulmonary fibrosis in animal models (fibrosis induced by bleomycin or irradiation) are of bone marrow origin and not derived from resident fibroblasts in the pulmonary interstitium [78–80]. Whether intra-alveolar myofibroblasts in organising pneumonia could also originate from bone marrow and not from resident interstitial cells is presently unknown. Furthermore, epithelial to mesenchymal transition has been recently emphasised [81].

The disappearance of myofibroblasts and fibroblasts in fibrosis may occur by apoptosis, possibly through loss of transforming growth factor-β signalling [82, 83]. Apoptotic activity is increased in the newly formed connective tissue in organising pneumonia [84].

Although several rather similar factors of matrix remodelling are present in both COP and UIP, the reasons for the opposing mechanisms of reversibility of fibrosis in COP and ongoing fibrosis in UIP are not yet established.

A DISTINCT ENTITY AMONG THE IDIOPATHIC INTERSTITIAL PNEUMONIAS

Although the pulmonary lesions in COP are mainly intra-alveolar, COP was included in the American Thoracic Society/European Respiratory Society International Consensus Classification of the Idiopathic Interstitial Pneumonias [85], particularly due to: 1) its idiopathic nature; 2) the possible confusion with other forms of idiopathic interstitial pneumonias (table 1), especially when the imaging pattern is infiltrative; and 3) histopathological features of interstitial inflammation in the involved areas. The previous terminology of BOOP was abandoned because the major process is organising pneumonia, with bronchiolitis obliterans being only a minor and accessory finding (which may even be absent).

Clinical features

For more information regarding the clinical features of COP please refer to [15–19, 86–101]. Males and females are equally affected by COP, with mean age of onset ~50–60 yrs. A few rare cases have been reported in children [102]. Nonsmokers or ex-smokers are affected approximately twice as often as smokers, but the proportion of nonsmokers may be higher among females [89], a finding which needs to be confronted with the prevalence of smoking in the different countries. However, COP is clearly a disorder not related to smoking. A seasonal (early spring) occurrence of COP with relapse every year at the same period has been reported [103]. Recurrent catamenial COP has also been mentioned [104].

Clinical manifestations begin with a mild flu-like illness with fever, cough, malaise and progressively mild dyspnoea, anorexia and weight loss. Dyspnoea may occasionally be severe, especially in the eventuality of rapidly progressive disease. Haemoptysis is uncommon and seldom severe [105]. Other uncommon manifestations include chest pain, night sweats and mild arthralgia (when arthralgia is prominent and/or associated with myalgia an underlying connective tissue disease should be suspected). Air leak (pneumothorax, pneumomediastinum) may be a rare presenting feature [106, 107]. Since the most common manifestations are nonspecific, diagnosis is often delayed (6–13 weeks). Physical examination usually discloses focal sparse crackles, but may be almost normal. There is no finger clubbing.

Imaging features

For more information about the imaging features of COP refer to [15–18, 90, 95, 96, 98, 100, 108–133]. The three main characteristic imaging patterns of COP consist of multiple alveolar opacities (typical COP), solitary opacity (focal COP), and infiltrative opacities (infiltrative COP) [17]. In a study of diagnostic accuracy of thin-section computed tomography (CT) in a series of patients with idiopathic interstitial pneumonias, the correct diagnosis of COP was the highest, in 79% of cases [134], suggesting that the CT imaging features are characteristic.

TABLE 1 Typical distinctive characteristics of cryptogenic organising pneumonia (COP), idiopathic nonspecific interstitial pneumonia (NSIP) and idiopathic pulmonary fibrosis (IPF)

	COP	Idiopathic NSIP	IPF
Histopathological pattern	Organising pneumonia	NSIP	Usual interstitial pneumonia
Histopathological features	Preserved lung architecture, intralumenal buds of granulation tissue in the distal airspaces (alveoli and alveolar ducts, possibly bronchioles); mild interstitial chronic inflammation; patchy distribution	Temporal and spatial homogeneity, mild-to-moderate interstitial inflammation (usually lymphocytic) with intra-alveolar organising fibrosis (minor component) and lack of interstitial fibrosis (cellular NSIP pattern); dense or loose interstitial fibrosis with mild or moderate interstitial chronic inflammation (fibrosing NSIP pattern)	Architectural destruction; temporal and spatial heterogeneity (areas of normal lung present); interstitial fibrosis with honeycombing; fibroblastic foci
Mean age yrs	50–60	40–50	60–70
Onset	Subacute	Chronic/subacute	Chronic
Clinical manifestations	Mild dyspnoea, cough, fever, sparse crackles; no finger clubbing	Moderate-to-severe dyspnoea, cough; diffuse crackles; finger clubbing uncommon	Severe dyspnoea, cough; severe restrictive ventilatory defect at lung function tests, with marked hypoxaemia; diffuse crackles; finger clubbing common
Imaging features#	Patchy areas of consolidation (peripheral, bilateral, possibly migratory, air bronchogram)	Ground-glass opacities and reticulation, basal predominance	Reticular abnormalities, honeycombing, traction bronchiectasis (peripheral, basal)
BAL	Mixed pattern (mild increase in lymphocytes, neutrophils, eosinophils)	Increase in lymphocytes (and possibly neutrophils)	Increase in neutrophils (and possibly eosinophils)
Prognosis	Excellent without sequelae	Very good (cellular pattern); rather poor (fibrosing pattern)	Poor
Response to corticosteroid treatment	Excellent	Usually good (cellular pattern); usually moderate or poor (fibrosing pattern)	Poor

BAL: bronchoalveolar lavage. #: high-resolution computed tomography.

Typical COP

Multiple alveolar opacities on imaging represent the most frequent and typical imaging features of COP (figures 3 and 4). These are usually bilateral and peripheral, and are often migratory. Their size varies from a few centimetres to a whole lobe, and an air bronchogram is often present in consolidated opacities. On a high-resolution computed tomography (HRCT) scan, the density of opacities ranges from ground glass to consolidation and more opacities are detected than on chest radiographs. This imaging pattern narrows the differential diagnosis, which mainly comprises the idiopathic chronic eosinophilic pneumonias, low-grade pulmonary lymphomas, and bronchioloalveolar lung carcinoma. Idiopathic chronic eosinophilic pneumonia is often associated with asthma and increased blood eosinophil level is present. However, it may overlap with COP, as in the figures of histopathological features reported in the series by CARRINGTON *et al*. [135], where typical buds of granulation tissue in addition to eosinophilic pneumonia are seen. Other cases of overlap of organising pneumonia and chronic eosinophilic pneumonia (idiopathic or not) have been reported [136–140]. Furthermore, increased level of eosinophils in BAL may be found in some patients with COP. In both disorders, relapses are common. The primary pulmonary lymphomas of low grade are also relatively responsive to corticosteroids (but not as rapidly as in COP). In bronchioloalveolar carcinoma, associated nodules are common and there is no regression with corticosteroids.

The typical imaging features of COP are usually so characteristic that they allow the possibility of diagnosis for most experienced clinicians.

Solitary focal opacity

This pattern is not characteristic and the diagnosis of COP is often made from histopathology of a nodule or a mass excised on suspicion of bronchogenic carcinoma [141] (fig. 5). However, organising pneumonia is distinct from round pneumonia improving with antibiotics [142–144]. Neutrophilic inflammation or microabscesses may be associated with the typical features of organising pneumonia [145, 146]. The lesions are often located in the upper lobes, and may be cavitary. The clinical presentation may be that of COP as described above, but focal organising pneumonia may be totally asymptomatic and discovered by routine chest radiographs (some patients may recall that they had a previous history of pneumonia) [17, 90, 145]. The suspicion of carcinoma may be increased by false-positive fluorodeoxyglucose positron emission uptake [147, 148]. Solitary focal organising pneumonia usually does not relapse after surgical excision. Possible spontaneous regression of solitary nodular organising pneumonia has been reported previously [149].

Infiltrative COP

Infiltrative COP is often associated with interstitial and superimposed small alveolar opacities on imaging (fig. 6).

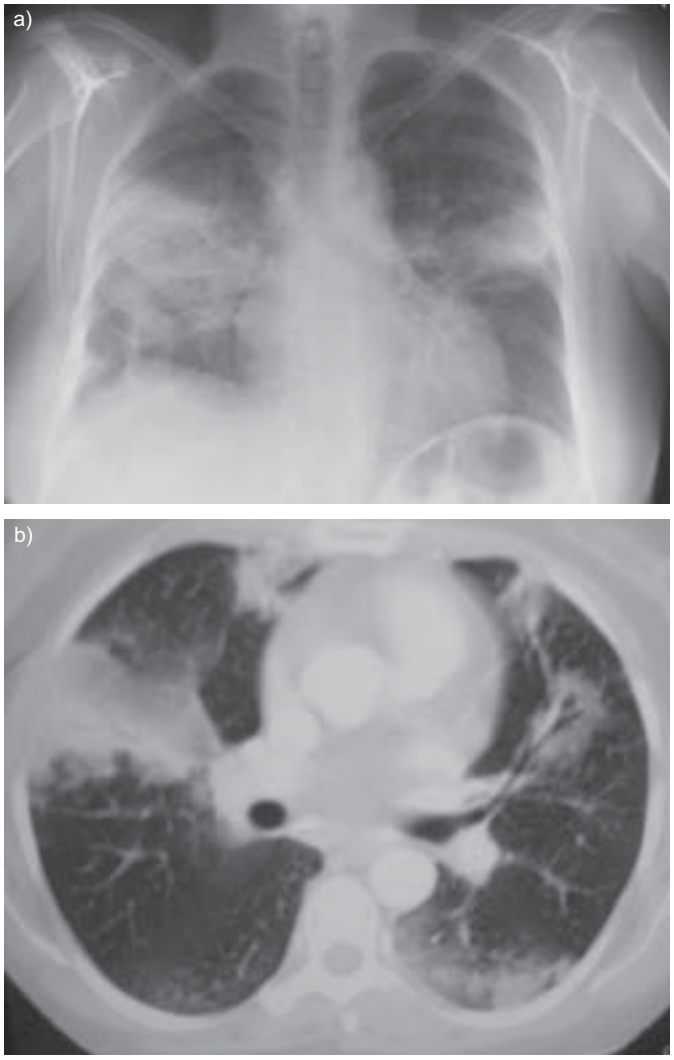

FIGURE 3. Typical cryptogenic organising pneumonia showing patchy bilateral alveolar opacities on a) chest radiograph and b) high-resolution computed tomography scan.

Some cases overlap with other types of idiopathic interstitial pneumonias, especially IPF and nonspecific interstitial pneumonia (NSIP). In the latter, focal areas of organising pneumonia are often encountered at histopathology [150, 151]. However, these are scattered foci, which are small and compose <10% of lesions, with interstitial pneumonia being the main lesion, whereas in organising pneumonia interstitial inflammation does not extend beyond the area of intra-alveolar fibrosis. The infiltrative pattern may consist of a poorly defined arcade-like or polygonal appearance defining a perilobular pattern [152], which is often associated with other opacities, especially consolidation.

Other imaging features

Several other imaging features have been reported [108]. The nodular pattern may consist of a well-defined ''acinar'' pattern with nodules of ~8 mm in diameter, or of a more subtle poorly defined (micro)nodular pattern. Multiple nodules of organising pneumonia may suggest metastatic lesions [153], especially

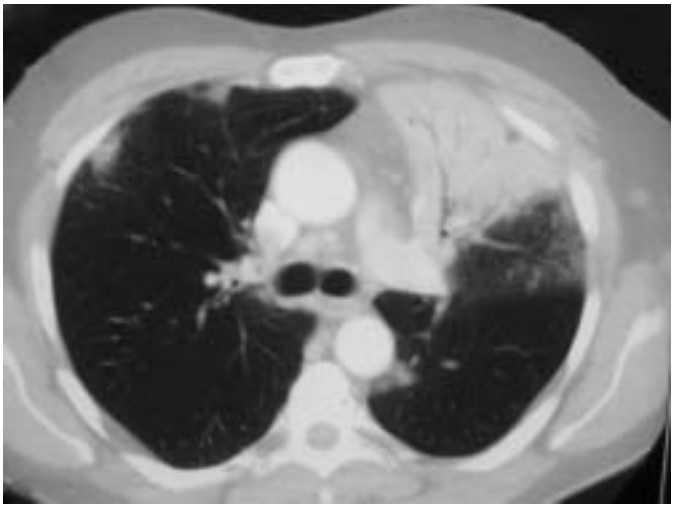

FIGURE 4. High-resolution computed tomography showing typical cryptogenic organising pneumonia with consolidation in the left-upper lobe with an air bronchogram. Of note are two small contralateral subpleural opacities.

in patients with a history of cancer. Some reported cases of cavitary COP correspond to consolidation superimposed on emphysema [154]. The bronchocentric pattern of COP is defined by areas of consolidation surrounding the bronchovascular bundles. The linear and band-like pattern consists of opacities extending radially to the pleura; some band-like opacities lie in the periphery of the lung parallel to the chest wall (the latter may be observed especially during the resolution of peripheral alveolar opacities). The halo sign [155], or particularly a reversed halo sign, of lung opacities have been reported [156]. Other imaging features consist of multiple masses or nodules (possibly excavated), and pneumatocele [132]. A diffuse micronodular pattern with histopathological features of bronchiolitis with peribronchiolar organising pneumonia has been reported [157]. Pleural effusion is seldom seen in COP, although it was present in 22% of cases in a previous series [90].

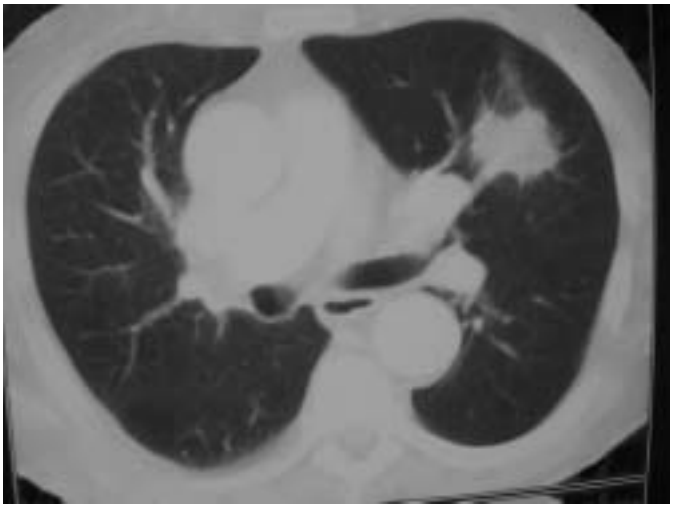

FIGURE 5. High-resolution computed tomography of cryptogenic organising pneumonia presenting as solitary focal opacity.

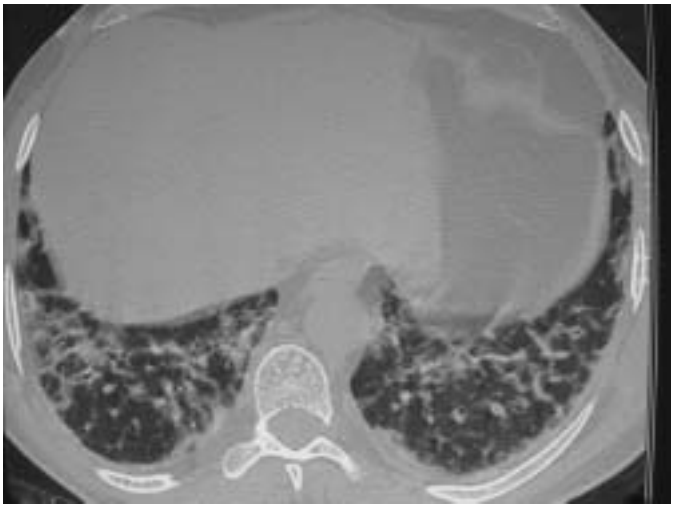

FIGURE 6. High-resolution computed tomography of cryptogenic organising pneumonia presenting as infiltrative lung disease.

Lung function tests

For more information about lung function tests in COP refer to [15–19, 95, 96, 98, 103, 114, 158, 159]. A mild or moderate restrictive ventilatory defect is the most common abnormality at spirometry. Airflow obstruction may be present in patients with a history of smoking and underlying chronic obstructive pulmonary disease. The transfer factor of the lung for carbon monoxide is reduced in proportion to restriction, but the transfer coefficient is usually normal. Hypoxaemia at rest and/or during exercise is usually mild. More severe hypoxaemia may be present in patients with widespread lung lesions and rapidly progressive disease. However, some patients have marked hypoxaemia (usually well tolerated) with possible orthodeoxia because of alveolar right to left shunting, as demonstrated by increased alveolar–arterial oxygen difference on breathing 100% oxygen and negative contrast echocardiography [160, 161]. This is likely to result from defective vasoconstriction in areas of nonventilated alveoli because of intra-alveolar buds occupying the entire lumen of alveoli.

Biological features

BAL is indicated in all cases where COP is suspected. First, it helps in excluding other diagnoses or determining a cause of organising pneumonia. Thus, it may disclose active infection or neoplastic disorders especially lymphoma and bronchioloalveolar carcinoma (immunocytological analysis may establish the monotype of lymphocytes characteristic of lymphoma). In COP, a mixed pattern at differential cell count may orientate towards the diagnosis. It consists of an increase in lymphocytes (20–40%), neutrophils (~10%) and eosinophils (~5%) with the level of lymphocytes higher than that of eosinophils [17, 94, 97, 110, 162–164]. A markedly elevated percentage of eosinophils (>25%) may suggest an overlap with idiopathic chronic eosinophilic pneumonia [18, 96, 99, 109, 138]. The finding of a few plasma cells and/or mast cells is remarkable in COP. The lymphocytes are activated and the CD4/CD8 ratio is usually decreased [162, 165, 166].

Blood tests do not make a significant contribution to the diagnosis of COP. A moderate leukocytosis is usual with an increase in neutrophils. There is no eosinophilia and the C-reactive protein level and erythrocyte sedimentation rate are increased.

Diagnosis of COP

The diagnosis of COP requires the establishment of a diagnosis of organising pneumonia, then the exclusion of any possible cause (which may be relatively evident or require more laborious aetiological inquiry).

Histopathological diagnosis of organising pneumonia

Histopathological diagnosis of organising pneumonia has been discussed previously elsewhere [167, 168]. Once a diagnosis of COP is suspected, obtaining lung tissue for histopathological study is necessary. The hallmark of organising pneumonia is the presence of buds of granulation tissue consisting of fibroblasts–myofibroblasts embedded in connective tissue (fig. 7). These may extend from one alveolus to the next through the interalveolar pores as described in a case of ''fibrinous pneumonia'' by KOHN [169], thus giving a characteristic ''butterfly pattern''. These buds often extend into the bronchioles and may obstruct the lumen (bronchiolitis obliterans of the proliferative type). Mild interstitial inflammation is present in areas of organising pneumonia, and foamy alveolar macrophages are present in those alveoli that are not filled by buds. It must be emphasised that the mere presence of some buds is not sufficient to make a diagnosis of organising pneumonia as the organisation of intra-alveolar exudates is a nonspecific process that may occur in a variety of inflammatory lung diseases [170]. This is why pathologists must search carefully for other lesions that could represent the main inflammatory process associated with foci of intra-alveolar fibrosis.

As mentioned previously, the histopathological pattern of NSIP (idiopathic or not) may comprise buds, as may that of Wegener's granulomatosis, where organising pneumonia is present in 54% [171] to 70% [172] of cases, with organising pneumonia being the main histological finding in some patients [173]. They may also be present in eosinophilic pneumonia, hypersensitivity pneumonitis [170, 174], pneumonia distal to obstruction (especially of neoplastic origin), abscesses, aspiration pneumonia [16, 175, 176], cystic fibrosis [177, 178], organising diffuse alveolar damage of any cause, pneumoconiosis [179], or in the vicinity of pleural plaques [180]. Furthermore, microbiological studies on lung tissue may be helpful, including special stains to exclude infection, especially opportunistic infection. It is clear that such a meticulous analysis requires a rather large piece of lung tissue.

Video-assisted thoracoscopy (VAT) allows biopsy of the lung in good conditions of security and allows pieces of tissue of sufficient size to be obtained from several lobes (especially when all lesions do not appear of the same type on HRCT) to exclude associated conditions or different patterns of interstitial pneumonia. Currently, VAT is a safe procedure that may be used in most patients.

However, before proposing VAT, transbronchial biopsies are recommended, since the finding of characteristic intra-alveolar buds at histopathological examination is sufficient in most cases to make a provisional diagnosis of organising pneumonia

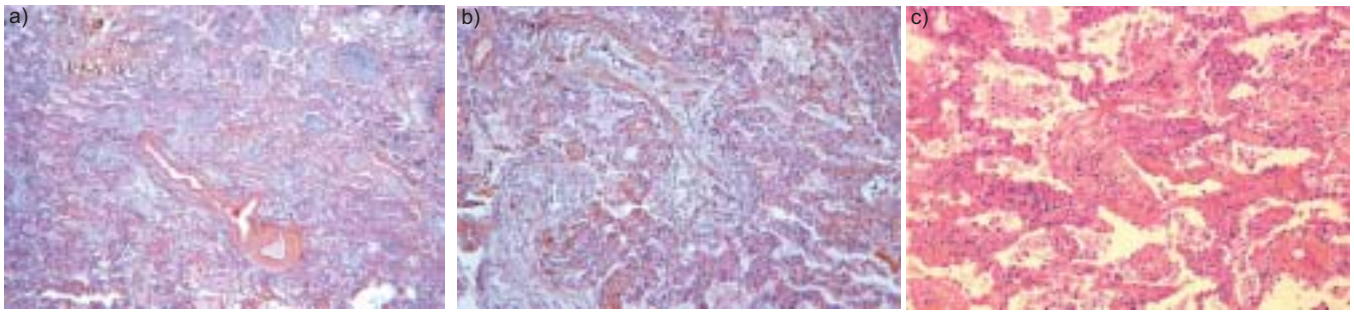

FIGURE 7. Histopathological features of organising pneumonia. a) Diffuse and prominent buds of granulation tissue represent the major histopathological pattern at low resolution. b) Typical intra-alveolar buds. c) Typical ''butterfly'' intra-alveolar bud. (All courtesy of L. Chalabreysse and F. Thivolet-Béjui, Dept of Pathology, Louis Pradel Hospital, Lyon, France).

[181, 182], thus allowing treatment in patients with typical imaging features and presumed good compliance for follow-up (hence allowing reconsideration of the diagnosis in the eventuality of unfavourable or atypical evolution under corticosteroid treatment). However, it must be remembered that the amount of lung tissue is relatively small and that the collapse and pinch artefacts induced by the forceps do not usually allow exclusion of other histopathological processes coexisting with foci of organising pneumonia. Therefore, atypical cases of COP diagnosed only on the basis of transbronchial biopsies need to be interpreted with caution, especially when imaging features are more suggestive of NSIP or IPF.

Whether a diagnosis of organising pneumonia may be accepted or not without histopathology and based only on clinical and imaging findings requires consideration, especially because it is increasingly frequent in clinical practice [86]. In patients too frail and/or too old to undergo lung biopsy, or refusing lung biopsy, corticosteroid treatment can be started provided patients have been informed that diagnosis is only probable and that a careful follow-up is programmed. Often rapid clinical and imaging improvement reinforces the probability of organising pneumonia. However, since long-term corticosteroid treatment often results in significant side-effects, some patients treated without histopathological confirmation sometimes question the diagnosis, eventually leading to later biopsy, especially on relapse.

Aetiological diagnosis: cryptogenic or not?

Organising pneumonia may be considered cryptogenic, a term used synonymously to idiopathic, although etymologically cryptogenic means of hidden cause and idiopathic means a self-governing disease; the disorder described is both cryptogenic and idiopathic. It is only considered to be cryptogenic when a definite cause or characteristic associated context is not present. Therefore, the aetiological diagnosis is of major importance before accepting the diagnosis of COP.

In non-COP, although some cases present with imaging and histopathological features quite similar to COP, other cases are more atypical especially as associated to histopathological features with more interstitial inflammation and/or fibrosis, and diffuse alveolar damage.

AETIOLOGY OF ORGANISING PNEUMONIA

The aetiological diagnosis of organising pneumonia attempts to establish a determined cause (as a single infectious agent), or a specific context known to be occasionally associated with organising pneumonia, such as connective tissue disease. Several possible causes and/or remarkable contexts may be associated. The clinical and imaging features of ''secondary'' organising pneumonia are similar to those of COP [90].

Determined causes of organising pneumonia

There are many determined causes of organising pneumonia. In addition to pneumococcal pneumonia, several other infectious agents (including bacteria, viruses, parasites and fungi) have been reported to cause organising pneumonia resulting from nonresolving pneumonia (table 2). Organising pneumonia, which improved with corticosteroids, was reported in a pregnant patient with HIV infection treated with lamivudine and zidovudine [205]. In clinical practice, the search for infection is not always exhaustive (sometimes because laboratory diagnostic tools such as serological tests or antigenuria are not available in all infectious disorders). Furthermore, some infections may initiate an uncontrolled inflammatory organising pneumonia process that persists after the aetiological agent has disappeared. An infectious agent may also induce a secondary noxious immunopathological process; a convincing example is rheumatic pneumonia [224, 225] where, in addition to the well known cardiac complications, typical organising pneumonia has been described [225–227], especially by MASSON *et al.* [227], who called the intra-alveolar buds ''bourgeons conjonctifs'' (connective tissue buds), terminology still used by some pathologists [228]. The clinical descriptions of rheumatic organising pneumonia have mentioned the ''fleeting nature'' of lung pneumonic opacities, improvement with adrenocorticotropin (ACTH), and even cited a case of ''rebound phenomenon after small doses of ACTH were discontinued'' [224].

Iatrogenic organising pneumonia may be drug-induced or radiation induced. Drug-induced lung disease comprises several clinical, imaging, and histological patterns including those of organising pneumonia [229, 230]. Several drugs (table 3) have been reported to cause iatrogenic organising pneumonia, with relatively convincing histopathological features. Causality has not been firmly established for many drugs,

TABLE 2 Infectious causes of organising pneumonia

Organism	Reference
Bacteria	
Burkholderia cepacia	[183]
Chlamydia pneumoniae	[184, 185]
Coxiella burnetii	[186, 187]
Legionella pneumophila	[95, 188–194]
Mycoplasma pneumoniae	[95, 189, 195–197]
Nocardia asteroides	[198, 199]
Pseudomonas aeruginosa	[200]
Serratia marcescens	[201]; in lung transplant recipient [200]
Staphylococcus aureus	In lung transplant recipient [200]
Streptococcus pneumoniae	[5, 6, 202]
Viruses	
Adenovirus	[203]
Cytomegalovirus	[203, 204]
Herpes virus	In lung transplant recipient [200]
HIV	[205–210]; in a pregnant patient using cocaine [205]; following highly active antiretroviral therapy introduction [211]
Influenza virus	[189, 212–214]
Parainfluenza virus	[215]
Human herpes virus-7	[216] after lung transplantation
Respiratory syncytial virus	Overlap of organising pneumonia and eosinophilic pneumonia [136]
Parasites	
Plasmodium vivax	[217]
Dirofilaria immitis	[218]
Fungi	
Cryptococcus neoformans	[219]
Penicillium janthinellum	[220]
Pneumocystis jiroveci	In patients with HIV infection [207, 221, 222]; in a lung transplant recipient [200]; in a liver transplant patient [223]; following highly active antiretroviral therapy introduction [211]

mainly because only isolated case reports have been published. A further difficulty results from the association of several possible causes related to the disorder for which the drug has been prescribed; for example, in patients after bone marrow graft for haematological malignancy, it is often difficult to know from among the drug(s) received, infection(s) induced by iatrogenic aplasia, and immunological and inflammatory processes associated with graft *versus* host disease, which of these actually caused organising pneumonia.

Organising pneumonia secondary to bleomycin treatment for malignancies may present with multiple pulmonary nodules on imaging, thus mimicking pulmonary metastases [242–246 289]. The crazy-paving pattern in bleomycin-induced organising pneumonia is uncommon [247].

A peculiar iatrogenic organising pneumonia is one that is ''primed'' by radiation therapy to the breast (tangential field radiotherapy) [109, 290–300]. It closely resembles COP and clearly differs from radiation pneumonitis, especially because it may involve nonirradiated areas of the lung and possibly be migratory. Therefore, it differs from organising pneumonia in radiation pneumonitis limited to the radiation field [299, 301]. Organising pneumonia primed by radiation therapy had an incidence of 2.5% in a series of 157 patients with breast cancer who underwent radiotherapy after breast-conservative surgery [292], and a 2.4% incidence in another series of 206 patients [300]. It usually develops within 9–16 months after radiation therapy [291, 296, 301], with the mean age of affected patients being ~60 yrs. As in COP, the patients present with fever, nonproductive cough, mild dyspnoea and peripheral alveolar opacities on chest imaging with a pattern of consolidation and further ground-glass opacities. Often initially unilateral and located in the irradiated lung, these are migratory in many patients. In BAL, a ''mixed pattern'' is present at differential cell count with a marked increase in lymphocytes (~40%), and a mild increase in neutrophils (~4–10%) and eosinophils (~3%). Mast cells are often present (~1–2%) [291, 293] and the CD4/CD8 ratio of lymphocytes is decreased [293]. Corticosteroid treatment results in rapid clinical improvement with clearing of the pulmonary opacities on imaging without significant sequelae, in contrast with radiation pneumonitis resulting in retractile consolidation with traction bronchiectasis. However, as in COP, relapses are frequent upon reducing (to daily doses of 5–10 mg prednisone) or stopping corticosteroids, with opacities in the same or other locations. Radiation-primed organising pneumonia is thus quite similar to COP. Interestingly, this peculiar iatrogenic organising pneumonia provides some insight into the pathogenesis of

TABLE 3 Drugs identified as a cause of organising pneumonia

Drug	Reference
5-Aminosalicylic acid	[231, 232]
Acebutolol	[233]
Amiodarone	[90, 230, 233–240]
Amphotericin B	[241]
Bleomycin	[18, 242–252]
Busulfan	[230, 253, 254]
Busulfan and cyclophosphamide	[230]
Carbamazepine	[255, 256]; in association with carbamazepine induced lupus [257]
Cephalosporin (cefradin)	[258]
Chlorambucil	[259]
Doxorubicin	Possible recall after radiation to the breast [260]
Fluvastatin	[261]
Gold salts	[262, 263]
Hexamethonium	[264]
Interferon-α	[264, 265]
Interferon-α2b, pegylated interferon α2b	[266]
Interferon-α + cytosine arabinoside	[267]
Interferon + ribavirin	[266]
Interferon-β1a	[268, 269]
L-tryptophan	[270]
Mesalazine	[271]; in patients with ulcerative colitis [272]
Methotrexate	[230]
Minocycline	[273]
Nilutamide	[274]
Nitrofurantoin	[230, 275, 276]
Phenytoin	[277]
Sirolimus	In renal [278] and cardiac [279] transplant recipients
Sotalol	[280]
Sulfasalazine	[231]; in a patient with Crohn's disease [281]; in a patient with rheumatoid arthritis [282]; in patients with ulcerative colitis [283, 284]
Tacrolimus	[285]
Ticlopidine	In a patient with giant-cell temporal arteritis [286]
Trastuzumab	[287]
Vinbarbital-aprobarbital	[288]

COP. Patients receiving radiation therapy to the breast develop bilateral alveolar lymphocytosis of similar intensity in both lungs within 15 days after completion of radiotherapy, regardless of whether the patients later develop pneumonitis or not [303–305]. This suggests that after lymphocytic alveolitis has been ''primed'' by radiation therapy, a second trigger or individual characteristics (either genetic or acquired) may be required for organising pneumonia to develop. Most patients receive concomitant medical treatment (especially chemotherapy and/or tamoxifen), but no definite role of the drugs used has been identified as increasing the risk of organising pneumonia. However, fever and cough developed in one patient who received radiation therapy to the breast while receiving transtuzumab, with alveolar opacities in both lungs on imaging. A biopsy of an alveolar opacity in the nonirradiated lung found a histopathological pattern of organising pneumonia [287]. The patient improved once transtuzumab was discontinued without adding corticosteroids. A patient who had received radiation therapy to the breast 10 yrs earlier developed severe organising pneumonia while receiving single-agent chemotherapy with doxorubicin [260], which might correspond to the phenomenon of ''radiation recall'' described with doxorubicin. The latter two cases represent examples of possible triggers for radiation-primed organising pneumonia. However, more common agents, such as respiratory infections, could also play a triggering role.

Some other causes of organising pneumonia have been reported. An epidemic of organising pneumonia due to the aerosolised textile dye Acramin FWN has been reported [306–309]. However, a number of patients were characterised by severe progressive disease (especially those with an infiltrative pattern on imaging) with irreversible fibrosis and ensuing death. These patients had a histopathological pattern including hyaline membranes and mural incorporation of intra-alveolar fibrosis, suggesting the organising stage of diffuse alveolar damage rather than typical organising pneumonia [306, 308]. Paraquat ingestion usually results in diffuse alveolar damage, but hyaline membranes were not present in a fatal case with intra-alveolar fibrosis [310]. Organising pneumonia has been

reported in association with cocaine use [311], including a case of a pregnant female with HIV infection [205].

Cavitating organising pneumonia was reported in a floor cleaner with an incidental heavy exposure to benzalkonium compounds; in addition, this patient had myeloperoxidase deficiency [312]. A spice process technician developed organising pneumonia of presumed occupational origin [313].

An aetiological role for gastro-oesophageal reflux with occult aspiration has been suggested in several cases [314, 315], but has not been convincingly demonstrated as a common cause of organising pneumonia when histopathological criteria of aspiration pneumonia (exogeneous lipid pneumonia with multinucleated foreign-body giant cells) are not present [175, 316]. Patchy organising pneumonia is a feature of middle lobe syndrome [317].

Organising pneumonia within a specific context

Organising pneumonia may develop in patients with a well characterised disorder of unknown cause, such as connective tissue disease. It may also occur secondary to lung transplantation or bone marrow grafting. In such situations, organising pneumonia is considered as a pulmonary manifestation of the inflammatory and/or immune process associated with the underlying condition, but the synergistic role of iatrogenic or infectious agents must be systematically evaluated. The aetiology of organising pneumonia in such conditions is likely to be plurifactorial.

Connective tissue disorders may comprise lung involvement of various types, especially interstitial lung disease, which usually develops during the course of disease, but which may also precede its recognition. In clinical practice, many patients with connective tissue disease and interstitial lung disease do not undergo lung biopsy. In patients with lung biopsy, NSIP is the most common histopathological pattern associated with scleroderma, dermatomyositis–polymyositis and rheumatoid arthritis. Organising pneumonia occurs particularly in patients with dermatomyositis–polymyositis [318–331], where it may be the presenting manifestation [212, 332]. In some patients it is associated with anti-JO-1 autoantibodies [324, 326, 333]. Organising pneumonia has also been reported in rheumatoid arthritis [158, 334–337], and more occasionally in systemic lupus erythematosus [338–341], scleroderma [342, 343], CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) syndrome with primary biliary cirrhosis [15, 344], and Sjögren syndrome [345, 346]. Abundant buds of organising pneumonia have been reported in association with NSIP in a patient with scleroderma [347].

In the connective tissue diseases, organising pneumonia may be the main histopathological feature, but a minor component of organising pneumonia may be associated with another histopathological pattern of interstitial pneumonia, especially NSIP. Overlap between organising pneumonia and eosinophilic pneumonia has also been reported [140, 319].

Organising pneumonia has increasingly been reported in patients after lung transplantation or bone marrow graft. The former terminology of COP (*i.e.* idiopathic bronchiolitis with organising pneumonia) was a source of confusion with bronchiolitis obliterans with airflow obstruction (obliterative bronchiolitis), which is the major cause of lung transplant failure and also a severe complication after allogenic bone marrow graft resulting from immune processes (namely transplant rejection and graft *versus* host disease, respectively). Several cases of organising pneumonia have been reported after lung transplantation [183, 200, 203, 348–351]. In this context, when not explained by a determined cause (such as infection, which is common in this immunosuppressed population), organising pneumonia may be considered as an associated or predominant pattern of acute lung rejection with or without concomitant ''pure'' bronchiolitis obliterans [200, 183, 200, 352, 353]. Furthermore, it is a risk factor for the bronchiolitis obliterans syndrome [350]. Organising pneumonia has also been reported after bone marrow graft [93, 354–366], where it is strongly associated with prior acute and chronic graft *versus* host disease [93, 357]. Some cases of organising pneumonia have also been reported after liver transplantation [367–369].

Organising pneumonia may occur in association with various haematological disorders or malignancies [90, 93] including: acute myelomonocytic leukaemia with inversion of chromosome 16 [370]; acute lymphoblastic leukaemia [371]; chronic myelomonocytic leukaemia [372]; myelodysplastic syndrome [354, 373, 374]; T-cell adult leukaemia [375, 376]; Evans syndrome [377]; Ewing sarcoma [371]; Hodgkin disease [371]; and various cancers with or without radiation therapy to the chest [378]. In patients with treated haematological malignancies and suspected invasive pulmonary aspergillosis, open lung biopsy may provide a diagnosis of organising pneumonia in up to ~20% of cases [379]. Organising pneumonia is frequently found in the vicinity of lung cancer [380], whether obstructive pneumonia is present or not. Obstructive pneumonia whatever its cause (*e.g.* foreign body inhalation) may comprise features of lipid pneumonia, chronic abscess and organising pneumonia. Coexistence of organising pneumonia with bronchioloalveolar carcinoma has been reported [381].

Although the most prevalent and distinctive pattern of respiratory involvement in inflammatory bowel disease (*i.e.* Crohn's disease and ulcerative colitis) is airway inflammation with ensuing bronchiectasis and/or obliterative bronchiolitis [382], organising pneumonia (focal or diffuse) is a well established manifestation of those disorders [231, 382–385]. Interestingly, the mononuclear cell infiltration in the pulmonary interstitium is denser and more uniform than in COP, suggesting a possible overlap with NSIP [231]. In contrast to patients with large airway disease, organising pneumonia does not manifest post-colectomy [231]. Since drugs used to treat these conditions may themselves cause organising pneumonia, the issue remains complex.

Ulcerative colitis suspected to have been transmitted from donor to recipient after allogeneic bone marrow transplantation in a patient with acute myeloblastic leukaemia developed concomitantly with organising pneumonia [361].

Other disorders with associated organising pneumonia include: common variable hypogammaglobulinaemia and other immunoglobulin deficiencies [386–388]; polyarteritis nodosa [389]; Sweet syndrome [390–392]; polymyalgia

rheumatica [393, 394]; Behçet disease [395]; thyroid disease (including cancer, Basedow disease, thyroiditis, hypothyroidism) [396]; and sarcoidosis (with organising pneumonia at the periphery of granulomatous lesions) [397]. It was also reported after coronary artery bypass graft surgery [398] or in association with localised giant inflammatory polyposis of the caecum and distal ulcerative colitis [399].

SEVERE AND/OR OVERLAPPING COP

One of the main characteristics of COP is its rapid improvement with corticosteroid treatment, both clinically and on imaging. Furthermore, COP is seldom life threatening at presentation. Nevertheless, some cases atypical for these features have been reported.

COP may present with widespread opacities on imaging and hypoxaemia, corresponding to the criteria for acute lung injury or the ARDS. Although hypoxaemia with alveolar right-to-left shunt may be well tolerated as mentioned previously, other patients may require mechanical ventilation (noninvasive or with tracheal intubation) or progress to death, especially when corticosteroid treatment is delayed [400, 401]. This occurs particularly in patients with delayed diagnosis who may improve once corticosteroid treatment is given (sometimes in association with immunosuppressive agents when corticosteroid resistance is suspected) [248, 402–407]. In some patients, underlying conditions or exposure (connective tissue disease, drugs, infection) are associated [248, 408].

Some patients, who may have underlying conditions or exposure, present with acute fibrinous and organising pneumonia, a recently described condition overlapping with ARDS both clinically and pathologically [409]. The onset is acute and progression may be fulminating or subacute. The dominant finding at lung biopsy is the presence of intra-alveolar fibrin in the form of ''fibrin balls'' without classic hyaline membranes. Some patients recover with treatment including corticosteroids, whereas other patients die.

This pathological pattern has also been reported upon autopsy of patients with severe acute respiratory syndrome [410] and in dermatomyositis [411]. The presence of fibrin in the organising lesions at lung biopsy of patients with COP has been associated with less complete recovery under corticosteroids [412].

Overlap with acute interstitial pneumonia (idiopathic) or ARDS (when a cause is present) is likely to explain the majority of cases of severe acute organising pneumonia with poor outcome. In such cases, the organising stage of diffuse alveolar damage may overlap with the histopathological features of organising pneumonia on lung biopsy [405, 413–419].

Rare cases of progression of COP to fibrosis and honeycombing have been reported, especially in patients with the infiltrative imaging pattern of organising pneumonia, and particularly when associated histopathological and imaging features of UIP are present [138, 248, 417, 420]. In some patients, acute exacerbation of idiopathic interstitial pneumonia may comprise organising pneumonia at lung biopsy [421]. Superimposed organising pneumonia was found on explant specimens from a patient with UIP who underwent lung transplantation [422]. Intra-alveolar organising lesions are common in the early fibrotic lesions in UIP [423]. Pathological predictors of unfavourable outcome in COP include scarring and remodelling of the background lung parenchyma, suggesting that some cases might fall into a category of subacute injury in UIP [424].

All of the previous situations correspond to cases of COP that are somewhat atypical, clinically and/or histopathologically. In such an eventuality, corticosteroid treatment should be instituted, but the outcome is uncertain.

TREATMENT OF COP

Corticosteroid treatment in COP results in rapid clinical improvement and clearing of the opacities on chest imaging without significant sequelae. However, relapses are common upon stopping or reduction of corticosteroids, thus often leading to prolonged treatment. Although the efficiency of corticosteroid treatment has long been established, as is usual in such so-called orphan diseases the precise dose and duration of treatment have not been established.

Initial doses vary from ~0.75–1.5 $mg \cdot kg^{-1} \cdot day^{-1}$, with further boluses of methylprednisolone on the first few days and a progressive decrease of dosage over the following weeks [89, 97, 425, 426]. The duration of treatment is not established, but 1 yr is often proposed.

Relapses are common, but their reported frequency depends on several parameters including the existence of underlying conditions or exposures in the published series, and the duration of treatment. It varies from 13% [90] to 58% of cases [89]. The current author's policy is to propose low doses of corticosteroids and a short duration of treatment, in order to avoid the side-effects of corticosteroids and treatment for long periods without necessity in patients who would not relapse [89]. Since relapses are not associated with increased mortality nor long-term functional morbidity, most informed patients accept an increased risk of relapse rather than having high doses of corticosteroids for up to 1 yr.

In a study of relapses in COP [89], the initial dose of corticosteroid to treat the first episode was 50 ± 17 mg. Relapses (2.4 ± 2.2) occurred in 58% of patients, with 19% having multiple (three or more) relapses. In total, 32% of patients had stopped treatment for a mean (median) delay of 9 ± 20 (2) months when the first relapse occurred. During the first relapse in the 68% of patients still receiving corticosteroids, the mean (median) dose was 12 ± 7 mg, with only one (4%) patient receiving >20 mg. The predictors of relapse included delayed treatment and mildly increased gamma-glutamyltransferase and alkaline phosphatase levels. A standardised treatment proposed by the Groupe d'Etudes et de Recherche sur les Maladies ''Orphelines'' Pulmonaires allowed a reduction in steroid doses; patients received 0.75 $mg \cdot kg^{-1}$ prednisone daily during 4 weeks, followed by 0.5 $mg \cdot kg^{-1}$ for 4 weeks, then 20 mg for 4 weeks, 10 mg for 6 weeks, and then 5 mg for 6 weeks before they were stopped. In severe cases, initial treatment consisted of *i.v.* boluses of prednisolone (2 $mg \cdot kg^{-1} \cdot day^{-1}$ for the first 3–5 days). Relapses while receiving prednisone at $\leqslant$20 mg daily were treated by increasing prednisone to 20 mg only, then decreasing as above. The severity of hypoxaemia as a determinant for the subsequent relapse [427] was not confirmed in the present series.

Occasional spontaneous improvement of crytogenic organising pneumonia, or response to treatment with antibiotics (especially macrolides) has been reported [16].

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