Rare diseases · 8

Organising pneumonia

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Organising pneumonia is defined pathologically by the presence in the distal air spaces of buds of granulation tissue progressing from fibrin exudates to loose collagen containing fibroblasts (fig 1).[1 2] The lesions occur predominantly within the alveolar spaces but are often associated with buds of granulation tissue occupying the bronchiolar lumen (bronchiolitis obliterans). This pathological pattern is not specific for any disorder or cause, but reflects one type of inflammatory process resulting from lung injury. It may also be a feature of the organising stage of adult respiratory distress syndrome and may be an accessory finding in other inflammatory disorders such as vasculitis. However, organising pneumonia is the particular pathological hallmark of a characteristic clinicoradiological entity called cryptogenic organising pneumonia. This terminology is preferred to the other name used for this condition—namely, idiopathic bronchiolitis obliterans with organising pneumonia (BOOP)—which may be confused with other types of bronchiolar disorders, particularly constrictive bronchiolitis obliterans which is mainly characterised by airflow obstruction.

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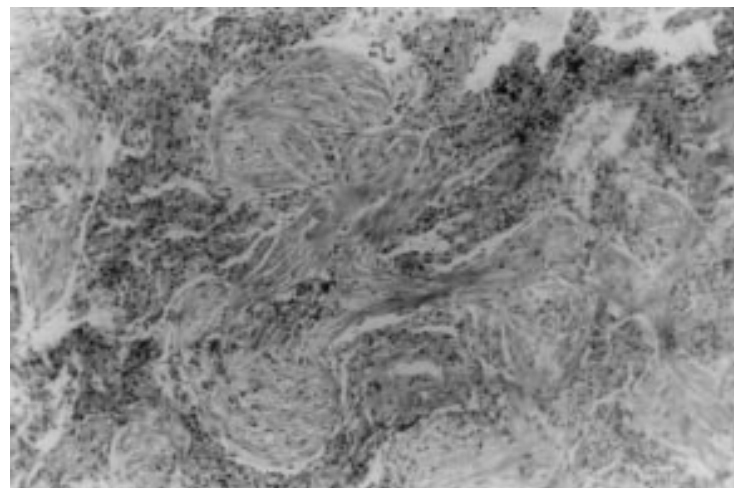
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Aetiology of organising pneumonia

Because organising pneumonia is a non-specific inflammatory pulmonary process, it may result from a number of causes. Pathologists may report features of organising pneumonia in association with conditions such as

Figure 1   Buds of granulation tissue in the distal air spaces defining organising pneumonia at histopathology.

infectious pneumonia, lung abscess, empyema, lung cancer, bronchiectasis, broncholithiasis, chronic pulmonary fibrosis, aspiration pneumonia (giant cells and foreign bodies usually are present), adult respiratory distress syndrome, pulmonary infarction, and middle lobe syndrome.[3 4]

Organising pneumonia may be classified into three categories according to its cause: organising pneumonia of determined cause; organising pneumonia of undetermined cause but occurring in a specific and relevant context; and cryptogenic (idiopathic) organising pneumonia. Several possible causes and/or associated disorders may coexist in the same patient. There are no clear distinguishing clinical and radiological features between cryptogenic and secondary organising pneumonia.[5]

ORGANISING PNEUMONIA OF DETERMINED CAUSE
Infection is a common cause of organising pneumonia. Indeed, the concept of organising pneumonia as a distinct pathological entity emerged at the beginning of the 20th century with its recognition at necropsy in patients dying from bacterial pneumonia, especially pneumococcal pneumonia.[6–10] It was interpreted as the failure of the usual resolution of pneumonia. Organising pneumonia has since been found in association with many other infections, mainly bacterial, but also in viral, parasitic and fungal infections (table 1). In bacterial infections organising pneumonia oc-

Table 1   Infectious causes of organising pneumonia

	Reference
Bacteria	
Chlamydia pneumoniae	169, 170
Coxiella burnetii	171
Legionella pneumophila	86, 125, 172–176
Mycoplasma pneumoniae	86, 125, 177
Nocardia asteroides	178, 179
Pseudomonas aeruginosa	62
Serratia marcescens	62, 180
Staphylococcus aureus	62
Streptococcus group B (newborn treated by extracorporeal oxygenation)	181
Streptococcus pneumoniae	6, 7, 182
Viruses	
Herpes virus	62
Human immunodeficiency virus	183–185
Influenza virus	125, 186
Parainfluenza virus	187
Parasites	
Plasmodium vivax	188
Fungi	
Cryptococcus neoformans	189
Penicillium janthinellum	190
Pneumocystis carinii (in AIDS)	62, 191, 192

Table 2 Drugs identified as causing organising pneumonia

	Reference
5-aminosalicylic acid*	69, 70
Acebutolol	193
Acramin FWN	194–196
Amiodarone	5, 193, 197–202
Amphotericin	203
Bleomycin	83, 137, 204–212
Busulphan	213, 214
Carbamazepine†	215
Cephalosporin (cefradin)	216
Cocaine	217
Gold salts¶	218, 219
Hexamethonium	220
Interferon alpha	220
L-tryptophan	221
Mesalazine	222
Minocycline	223
Nilutamide	224
Paraquat	225
Phenytoin	226
Sotalol	227
Sulfasalazine*	69, 228–230
Tacrolimus	231
Ticlopidine**	232
Vinabarbital-aprobarbital	233

*In patients treated with this drug for ulcerative colitis or Crohn's disease which may themselves be associated with organising pneumonia. †In the course of lupus syndrome induced by the drug. ¶In patients with rheumatoid arthritis which may itself be associated with organising pneumonia. **In a patient with temporal arteritis.

curs mostly in non-resolving pneumonia where, despite control of the infectious organism by antibiotics, the inflammatory reaction remains active with further organisation of the intra-alveolar fibrinous exudate. Rheumatic pneumonia occurring during the course of rheumatic fever was recognised as a typical organising pneumonia with intra-alveolar buds described as "bourgeons conjonctifs" or Masson's bodies.[11 12]

With drug induced organising pneumonia it is sometimes difficult to determine causality since organising pneumonia may also be associated with the underlying disease (a connective tissue disease, for example). Resolution of organising pneumonia after stopping the drug is obviously the best clue to establish causality. In many cases, however, it is not possible to determine whether the drug is responsible or not—for example, in patients with cancer or haematological malignancies who may be treated with several drugs that are able to induce organising pneumonia.[5] Serious diagnostic pitfalls may occur with drug induced organising pneumonia—for example, bleomycin induced organising pneumonia which may present as pulmonary nodules resembling metastases in patients treated for aggressive and potentially metastatic cancers (table 2).

It has long been known that radiation therapy to the chest may induce radiation pneumonitis, an inflammatory reaction within the radiation field with some pathological features of organising pneumonia.[13 14] However, a syndrome similar to cryptogenic organising pneumonia has been identified recently in women receiving radiation therapy to the breast after removal of a malignant tumour.[15–22] It differs strikingly from usual radiation pneumonitis in that the pulmonary infiltrates occur or migrate outside the radiation fields and in the good response to corticosteroid

treatment. The pathological findings are typical of organising pneumonia. Bronchoalveolar lavage (BAL) fluid differential cell counts show an increase in lymphocytes in particular, but also in neutrophils, eosinophils, and mast cells. Although corticosteroid treatment is usually necessary, spontaneous improvement may occur.[20] Interestingly, unilateral breast irradiation, whether or not it results in pneumonitis, has been shown to induce bilateral lymphocytic alveolitis with activated CD4+ T cells[23 24]; however, this does not result in organising pneumonia in the majority of patients. An additional genetically determined host factor and/or trigger acting on radiation "primed" lymphocytes may be necessary to induce the organising pneumonia syndrome.[15 19]

ORGANISING PNEUMONIA OF UNKNOWN CAUSE OCCURRING IN A SPECIFIC CONTEXT

The connective tissue disorders often involve the pulmonary parenchyma. Infiltrative lung disease in this context varies and may include usual interstitial pneumonia, non-specific interstitial pneumonia, or organising pneumonia. The idiopathic inflammatory myopathies may cause a characteristic organising pneumonia syndrome.[25–36] Organising pneumonia also occurs in rheumatoid arthritis[5 22 37–43] and Sjögren's syndrome[44 45] but, in contrast, is uncommon in systemic lupus erythematosus[40 46–49] and systemic sclerosis.[5 50 51] In addition to organising pneumonia, bronchiolitis obliterans may occur in connective tissue disorders (particularly in rheumatoid arthritis).[52]

Pathological features of organising pneumonia may occur with Wegener's granulomatosis. These usually consist of small foci of organising pneumonia at the periphery of otherwise typical granulomatous lesions, but in some cases they are the major histological finding although the patients do not differ clinically or radiologically from those with classical Wegener's granulomatosis.[53] Organising pneumonia has been reported occasionally in polyarteritis nodosa.[54]

It is well established that both lung transplantation and bone marrow grafting may be complicated by constrictive mural bronchiolitis with airflow obstruction. This is generally interpreted as a manifestation of chronic rejection and graft versus host disease, respectively, and it often results in severe chronic obstructive respiratory failure. Less commonly, organising pneumonia occurs in transplanted lungs.[55–61] Organising pneumonia in this setting may result from preservation injury, infection or aspiration, or it may be a manifestation of lung rejection[57 61 62] and it may be associated with chronic rejection associated bronchiolitis obliterans.[57] In lung transplant patients the combination of constrictive obliterative bronchiolitis and organising pneumonia appears to be associated with a poorer prognosis than constrictive obliterative bronchiolitis alone.[59] Organising pneumonia also occurs after allogeneic bone marrow grafts[63–66] where it is considered to be a manifestation of graft versus host disease.[63]

Other disorders that have been reported to be associated with organising pneumonia include Sweet's syndrome,[67 68] ulcerative colitis,[69 70] Crohn's disease,[69] polymyalgia rheumatica,[71 72] thyroiditis,[43] Behçet's disease,[43] mesangiocapillary glomerulonephritis,[73] myelodysplasia,[74] leukaemia, myeloproliferative disorders, cancer,[63 75–77] common variable immunodeficiency,[78] and hepatitis C.[79] Since only single or small numbers of cases have been reported, it is unclear whether these represent a true association or whether the organising pneumonia results from other causes such as undiagnosed infection or drug induced reaction.

CRYPTOGENIC ORGANISING PNEUMONIA

Although organising pneumonia may result from numerous causes or occur in the context of systemic disorders, it remains cryptogenic and solitary in many cases. The recognition of cryptogenic organising pneumonia (COP) as a clinicopathological entity was long delayed for several reasons.[80] Pathologists used to consider organising pneumonia as a non-specific finding of little, if any, interest, and merely a consequence of previous unrecognised infection. When mentioned in pathological reports it was not accorded attention by clinicians. With the increased use of lung biopsies, organising pneumonia was identified more often but included in the vast group of interstitial lung disorders. COP was therefore only recognised as a distinct disorder in the early 1980s after the reports of Davison *et al*[81] and Epler *et al*.[82] Further studies in the 1980s[83 84] described its characteristic features, and COP is now accepted as a rare but very characteristic clinicopathological entity in pulmonary medicine.

Clinical characteristics[5 40 43 63 81–90]

Men and women are affected equally in most series and are usually aged between 50 and 60 years (with a range from about 20 to 80). Occasional cases in adolescents have been reported.[91] No predisposing factors have been identified and, in particular, organising pneumonia is not related to smoking (most patients are non-smokers or ex-smokers). Seasonal cases (late February to early May) with biochemical cholestasis were found in one study,[92] but this has not been further reported.

The onset of symptoms is usually subacute with fever, non-productive cough, malaise, anorexia, and weight loss. Haemoptysis, bronchorrhoea, chest pain, arthralgia, and night sweats are uncommon. Severe haemoptysis is exceedingly rare.[93] Dyspnoea is usually mild and only on exertion but it is occasionally severe in some acute and life threatening cases. In most cases symptoms develop over a few weeks after a viral like illness and diagnosis of COP is usually made after 6–10 weeks. Physical examination may be normal, but sparse crackles are commonly found over affected areas.

Figure 2 Typical imaging pattern of organising pneumonia with patchy alveolar opacities on chest radiograph.

Imaging[5 22 81–83 86 87 89 92 94–117]

Although the imaging pattern of COP is heterogeneous, the radiographic and computed tomographic (CT) findings are often so characteristic that they suggest the diagnosis. Three main imaging patterns may be distinguished.

The most frequent and typical imaging profile of COP is of multiple patchy alveolar opacities with a peripheral and bilateral distribution (fig 2). These opacities often migrate spontaneously. Their size is variable, ranging from a few centimetres to a whole lobe. On the CT scan the density of the opacities varies from ground glass to consolidation; an air bronchogram may be present in consolidated areas (fig 3). This imaging pattern, although highly suggestive of COP, is not specific and the differential imaging diagnosis comprises conditions such as the chronic eosinophilic pneumonias (which can occur with COP), primary low
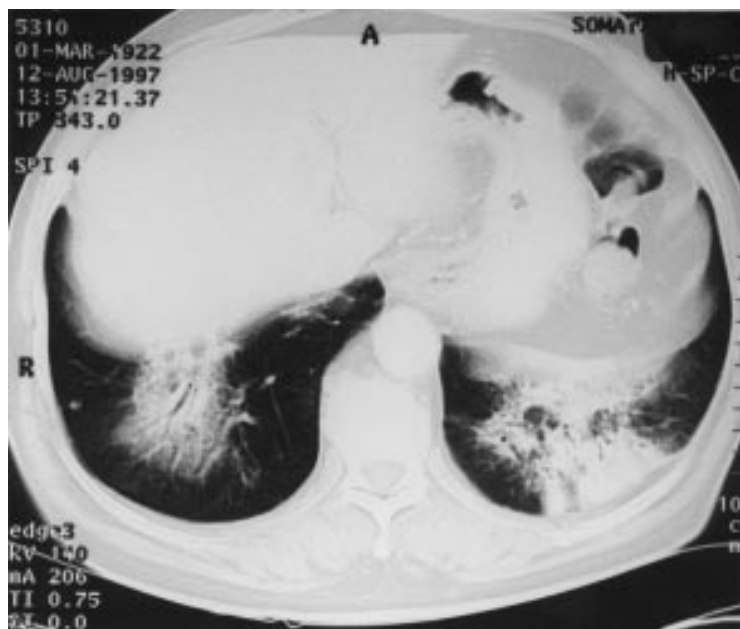

Figure 3 Typical imaging pattern of organising pneumonia with patchy consolidation in the lower lobes containing air bronchograms on computed tomographic scan.

grade pulmonary lymphomas, and bronchiolo-alveolar carcinoma.

The two other common imaging patterns of COP are less characteristic. Some patients present with a diffuse bilateral infiltration (fig 4) usually associated with interstitial opacities and small superimposed alveolar opacities. These patients show a greater degree of interstitial inflammation in addition to intra-alveolar organisation on pathological examination. Since intra-alveolar organisation is a non-specific feature that may be found in a variety of interstitial disorders, some cases may overlap with the organising stage of diffuse alveolar damage, non-specific interstitial pneumonia, or cryptogenic fibrosing alveolitis.

COP may also present on imaging as a solitary focal lesion associated usually with sub-acute or chronic inflammatory illness. This is often a pathological diagnosis after surgical

Figure 4   Diffuse infiltrative pattern of organising pneumonia with interstitial and small alveolar opacities on computed tomographic scan.
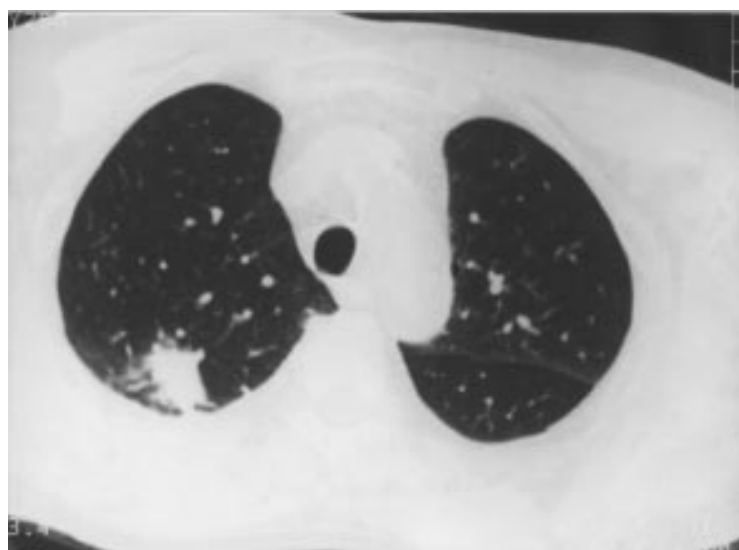

Figure 5   Solitary focal mass in the right upper lobe. This pattern may be diagnosed as lung cancer.

excision of a lesion suspected to be a lung cancer on a routine chest radiograph; it usually occurs in the upper lobes (fig 5) and may cavitate. Some cases probably correspond to unresolved pneumonia.[5 22 40 84 95 112]

Less common radiological findings in patients with COP include crescentic opacities surrounding areas of ground glass attenuation, multiple or cavitary nodules or masses, pneumatocele, peripheral irregular subpleural bands in parallel with the pleural surface, and bronchial dilatation (in association with opacities). Large nodules may have irregular or spiculated margins and a relatively broad pleural tag.[118] Pleural effusion is generally uncommon although it was present in 22% of patients in one series.[5]

Lung function tests[40 81–84 86–88 92 97 101 119]
The most common finding on lung function testing in patients with COP is a mild or moderate restrictive ventilatory defect. Airflow obstruction may be present in smokers but is not a characteristic of COP (in contrast with the often severe airflow obstruction found in constrictive bronchiolitis obliterans). The transfer factor for carbon monoxide is reduced, but the transfer coefficient may be normal. Mild hypoxaemia at rest and/or on exercise is common. Hypoxaemia is occasionally severe and correlates with right to left shunting as shown by increased alveolar-arterial oxygen difference while breathing 100% oxygen (unpublished personal data). Severe hypoxaemia in COP may reflect widespread and severe pulmonary disease or shunting in more limited lesions, or both.

Bronchoalveolar lavage and laboratory findings
Bronchoalveolar lavage may be used to exclude other disorders or causes of COP, particularly infections. The differential white cell count may show a characteristic "mixed pattern" with increased lymphocytes (20–40%), neutrophils (about 10%), and eosinophils (about 5%), sometimes with some plasma cells or mast cells.[5 84 89 120–122] The lymphocyte CD4/CD8 ratio is decreased.[90 120 123 124]

There are no specific laboratory findings in COP. The erythrocyte sedimentation rate and C reactive protein levels are increased, with the erythrocyte sedimentation rate being >60 mm in about 30% of patients.[5 81 84 89 124] There is a moderate leucocytosis, with an increased proportion of neutrophils.

Diagnosis of cryptogenic organising pneumonia
The diagnosis of COP relies on finding typical pathological and clinicoradiological features and the exclusion of any recognised cause or associated disorder. Pathological examination of lung specimens shows intra-alveolar buds of granulation tissue associated with fibroblasts, myofibroblasts, and loose connective tissue. Inflammatory cells may be present in the granulation tissue, especially during the early stages of the process (see below). The buds may extend from one alveolus to the next through the pores of Kohn (which were initially

described in this condition), giving a rather characteristic "butterfly" pattern. Foamy macrophages are conspicuous in empty alveoli. The lung structure is not disorganised. Bronchiolar lesions consist of similar plugs of granulation tissue inside the airway lumen in continuity with lesions in the alveoli and with only limited inflammation in the bronchiolar wall. The plugs of granulation tissue in organising pneumonia occupy the more distal air spaces.[1 40 125 126] This distribution is strikingly distinct from another type of bronchiolocentric lesion consisting of bronchiolitis obliterans with organising pneumonia limited to the alveoli adjacent to the involved bronchioles, thus giving a miliary pattern on the chest radiograph (Cordier and Loire, unpublished data).

For COP to be diagnosed the organising pneumonia should be the main pathological feature and not merely an accessory to other well defined lesions such as vasculitis, eosinophilic pneumonia, hypersensitivity pneumonitis, or non-specific interstitial pneumonia.[1 127] Furthermore, a careful search for a possible cause of organising pneumonia is necessary, including special stains to detect infectious agents.

Because the pulmonary lesions are often migratory and may resolve spontaneously, a chest radiograph just before the biopsy is necessary.

Video-assisted thoracoscopic lung biopsy is the currently preferred technique for diagnosing organising pneumonia since it provides quite large lung specimens which allow the diagnosis to be made with confidence and makes it easy to search for other pathological features. Transbronchial lung biopsy specimens may show organising pneumonia in many cases[5 128–130] but they do not adequately allow the exclusion of associated lesions or disclose clues to a cause for the process. We consider therefore that the diagnosis of organising pneumonia by transbronchial biopsy may be accepted only in typical cases and requires careful patient follow up to prompt a surgical biopsy if the initial diagnosis has to be reconsidered because the evolution of the illness is unusual. Most cases require a surgical lung biopsy specimen to be taken before starting treatment.

The diagnosis of COP without a biopsy is seldom justified. It may be considered in patients who are critically ill (particularly older patients) or if the clinical diagnosis is considered as highly probable by an experienced physician. Particularly careful follow up would be necessary in such patients and lack of improvement with corticosteroids or relapses despite relatively high doses of corticosteroids (over 25 mg per day) should lead the clinician to suspect other diagnoses, particularly lymphomas.[131]

Treatment and prognosis of organising pneumonia

Spontaneous improvement occurs occasionally in organising pneumonia[91 97 118] and slow improvement has been reported in some patients after prolonged treatment with erythromycin.[132] However, corticosteroids are the current standard treatment, although the ideal dose and duration necessary for complete healing are less certain.[87 90 133] The response to corticosteroids is impressive, although much less dramatic than in idiopathic chronic eosinophilic pneumonia. Clinical manifestations improve within 48 hours but complete resolution of radiographic pulmonary infiltrates usually takes several weeks (usually without significant sequelae). Most patients show a marked improvement after one week of treatment.

Although some authors recommend starting treatment with doses of prednisone of 1–1.5 mg/kg/day for 1–3 months,[133 134] in patients with typical COP we start with a lower dose of 0.75 mg/kg/day. Relapses involving the initial sites or different locations occur frequently as the dose of corticosteroid is reduced.[5 79 81 82 84 89 92 109 135] The final outcome is not significantly affected by the occurrence of relapses.[135] The severity of hypoxaemia at first presentation has been reported to be a determinant of subsequent relapse[79] but we could not confirm this finding.[135] The duration of treatment required varies considerably but is usually between six and 12 months. Some patients experience several relapses and require treatment for much longer. Because of the adverse effects of prolonged and high doses of corticosteroids, we try to withdraw them after a few months and only prolong treatment in patients with relapsing disease.

The prognosis in typical COP with patchy alveolar opacities is usually excellent following treatment with corticosteroids.[82 84 88 89 98 136] The prognosis of organising pneumonia secondary to a determined cause or associated with a specific condition such as a connective tissue disease is more difficult to determine because of the heterogeneity of reported cases. The prognosis in COP is usually better than that seen in secondary organising pneumonia,[5] probably due to the nature of the underlying disorders.

There are reports of patients with severe and rapidly progressive COP[137 138] but interpretation of such reports is unclear. Of 10 patients with rapidly progressive organising pneumonia characterised by severe respiratory failure and organising pneumonia on the initial pulmonary biopsy, subsequent pathological examination of the lung at autopsy in six showed a fibrotic honeycomb pattern.[137] In another series of patients with acute and life threatening organising pneumonia, organising adult respiratory distress syndrome (ARDS) was considered likely.[138] Some cases with a poor outcome may represent an uncommon evolution of otherwise typical organising pneumonia, but most are likely to be either acute interstitial pneumonia or organising ARDS, widespread organising pneumonia resulting in respiratory failure, organising pneumonia associated with other chronic disease or lung injury either aggravated by lung biopsy or associated with delayed treatment.[5 63 137–140] Some patients with severe disease requiring assisted ventilation may

improve completely with corticosteroids.[140] Factors that appear to be associated with a poor outcome in COP include a predominantly interstitial pattern on imaging, lack of a lymphocytosis on the BAL fluid differential cell count, associated disorders,[136] and a finding on histological examination of scarring and re-modelling of the lung parenchyma in addition to organising pneumonia.[141]

Cytotoxic drugs, especially cyclophosphamide and azathioprine, are occasionally used to treat COP,[90 134 137 139 142] but they have not been evaluated. The cytotoxic drugs are usually given in addition to corticosteroids so whether the observed improvement is due to the prolonged course of corticosteroids or to the cytotoxic drug is not known. Cyclophosphamide may be considered in severely ill patients who show no improvement with corticosteroid treatment within a few days and in patients who fail to improve despite a prolonged course of corticosteroids. In such acute and severe cases our usual practice is to give one to three intravenous boluses of cyclophosphamide, as in the initial treatment of Wegener's granulomatosis.[143]

Pathogenesis of organising pneumonia

Organising pneumonia is the pathological hallmark of a distinct type of lung injury and repair rather than a disease with one defined aetiology. The histopathophysiology underlying organising pneumonia can be seen as a blueprint of a pulmonary type of "wound healing" that results in a serious lung disorder.[144 145]

Organising pneumonia was described initially as a failure of resolution of acute pneumonia. Laennec[146] defined the usual pathological course of acute lobar pneumonia, later identified as pneumococcal pneumonia, as a sequence of congestion, hepatisation (when the appearance of the lung resembled the liver), followed by resolution without sequelae. The corresponding histological sequence comprised oedema rich in pneumococci and inflammatory cells, fibrin deposition within alveoli and, finally, liquefaction of fibrin by neutrophils and macrophages. Resolution of pneumonia did not occur in all cases, however, particularly before the era of antibiotics. Organisation of the inflammatory fibrinous exudates in the alveoli was described precisely in such cases, with the identification of the fibroblast as the main cell type involved in the process of organisation.[6 7 9 147] Apart from a direct infectious cause, organising pneumonia has also been found in rheumatic pneumonia[11 12 148 149] as a result of pulmonary inflammation comparable to the inflammatory process of carditis. Masson *et al*[11] described the intra-alveolar *bourgeons conjonctifs*, also called Masson bodies, in rheumatic pneumonia. It was clearly shown that these were not specific to rheumatic pneumonia but were present in a number of inflammatory disorders.[12]

The process of intra-alveolar organisation has been studied mainly in experimental animal models and in human ARDS. It results from a sequence of alveolar injury, intra-alveolar clotting with deposition of fibrin, and subsequent colonisation by fibroblasts to pro-duce a connective matrix.[144 150] The injury to both capillary endothelial cells and alveolar epithelial cells results in the leakage of plasma proteins, especially coagulation factors, into the alveolar lumen. Activation of the extrinsic pathway of the coagulation cascade is triggered by tissue factor and results in fibrin deposition. The metabolism of fibrin in the alveolar lumen and on alveolar surfaces results from the complex balance between the local procoagulant activity and the fibrinolytic processes. Increased procoagulant activity and decreased fibrinolytic activity result in the intra-alveolar coagulation of the exuded coagulation proteins, fibrin deposition, and alveolar damage. The migration and invasion of fibroblasts involves the cell surface matrix receptor CD44[151] and is blocked by anti-CD44 antibodies. In addition to building a provisional matrix for the continuation of the organisation process, the coagulation proteins and their degradation products exert a number of biological activities (especially chemotactic, activating, and proliferation promoting activities[152–154]) on fibroblasts, smooth muscle cells, and inflammatory cells.

The histopathophysiology of COP is a model of a lung fibroinflammatory process.[144] The first step consists of acute alveolar epithelial injury with cell necrosis and denudation of the basal laminae.[155–157] Organisation begins with the formation of intra-alveolar fibrinoid inflammatory cell clusters rich in coagulation factors and further intra-alveolar migration of interstitial fibroblasts through gaps in the injured basal laminae. The proliferating fibroblasts colonise the fibrin strands. They undergo phenotypic modulation into myofibroblasts and organise into fibroinflammatory buds with deposition of a loose connective matrix in which fibronectin and collagen III are abundant. The buds become progressively more fibrotic with concentric layers of myofibroblasts and connective tissue, thus giving the typical appearance of intra-alveolar buds.[155 157–159] The alveolar architecture is remarkably preserved, with the intraluminal buds extending into some alveolar ducts and bronchioles. Alveolar collapse and mural incorporation of the buds may be present in some areas, depending on the degree of initial alveolar damage.

An experimental model of BOOP has been developed recently in CBA/J mice infected with reovirus 1/L.[160] Respiratory infection by reovirus 1/L does not give rise to BOOP in CD-1 and BALB/c mice, suggesting that genetic host factors are important determinants of the development of the fibrotic response of the BOOP type. In this model increased numbers of macrophages are observed in the lungs of the mice within the first week after inoculation with the virus, and these express reovirus proteins. Increased numbers of macrophages persist during the three week course of the pulmonary disease, but whether they continue to express reovirus proteins after infectious virions can no longer be detected is not known.

Tissue factor antigen is expressed in COP, mainly in hyperplastic type II pneumocytes.[161] Anti-adhesive glycoproteins have been studied

in organising pneumonia. Tenascin is present throughout the extracellular matrix of the intra-alveolar buds whereas SPARC is only observed intracellularly in fibroblasts, and thrombospondin 1 forms a ring at the periphery of the buds, just beneath the epithelium from which it is probably produced. However, the role of these anti-adhesive proteins is still unclear.[162] Increased expression of interleukin-8 and fibronectin genes by alveolar macrophages have been reported in COP, suggesting that the inflammatory pulmonary process may be initiated and/or perpetuated by inflammatory cytokines produced in situ by alveolar macrophages.[163] Increased platelet-derived growth factor (PDGF) positive cells have been demonstrated by immunohistochemistry in organising pneumonia lesions and attributed to the local recruitment of monocytes into the foci of connective tissue proliferation.[164]

How corticosteroids induce the disappearance of the well organised fibrotic intra-alveolar buds remains a mystery. Degradation of the connective matrix requires specific enzymes such as matrix metalloproteinases (MMP), gelatinases, and stromelysins. These enzymes may be produced by leucocytes and the fibroblasts themselves. Cytokines may modulate the production of MMP-1 (collagenase) by fibroblasts,[165 166] and the composition of the matrix itself may modulate the production of proteases by fibroblasts.[167] Relaxin, a cytokine/growth factor, stimulates the expression of MMP-1 in a biphasic, dose dependent manner.[168] Thus, fibroblasts may play a role in the degradation of the matrix they themselves previously built.

Taken together, the clinical, pathological, and biopathological data suggest that COP reflects the response to an initial injury of unknown cause(s) which causes pulmonary inflammation, which is further self-perpetuated in some patients to produce the characteristic buds of intra-alveolar granulation tissue associating (myo)fibroblasts and connective matrix. The most intriguing feature of COP is its rapid resolution following treatment with corticosteroids, the mechanism of which is currently unknown.

Conclusion and research perspectives

Although rare, COP is now a well characterised entity with characteristic clinical and radiological features and pathological diagnostic criteria. Although treatment with corticosteroids is very effective, we are unable to predict which patients will relapse after reducing or stopping treatment, nor do we know the most appropriate dose with which to start treatment and how long patients should be treated. Some patients are probably overtreated whereas others would benefit from longer treatment. There may not be a single cause of COP but biopathological studies are needed to identify the mechanisms whereby a limited wound healing reaction switches to an idiopathic persistent inflammatory process which is nevertheless very responsive to corticosteroids.

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