

Cryptogenic organizing pneumonia

Authors: Professor Jean-François Cordier^{1,2}, Professor Ulrich Costabel¹, Professor Roland M. du Bois¹

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¹members of the European editorial committee of Orphanet encyclopedia

²Service de pneumologie - Centre des Maladies Orphelines Pulmonaires, Hôpital cardiovasculaire et pneumologique Louis Pradel, 28 Avenue du Doyen Lépine, 69677 Bron Cedex, France.

jean-francois.cordier@chu-lyon.fr

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Abstract

Cryptogenic organizing pneumonia (COP) or bronchiolitis obliterans with organizing pneumonia (BOOP) is an inflammatory lung disease with distinctive clinical, radiological and pathological features. The onset of symptoms is usually subacute with fever, nonproductive cough, malaise, anorexia and weight loss. Dyspnea, usually mild, is occasionally severe in some acute and life-threatening cases. Men and women are affected equally and are usually aged between 50 and 60 years. No predisposing factors have been identified. In most cases, symptoms develop over a few weeks and the diagnosis of COP is made after 6 to 10 weeks. In COP the organizing pneumonia is the most conspicuous pathological feature, examination of lung biopsy specimens shows intra-alveolar buds of granulation tissue consisting of fibroblasts, myofibroblasts, and loose connective tissue. The radiographic and computed tomography scan findings suggest the diagnosis when multiple patchy alveolar opacities with a peripheral and bilateral distribution are present. Video-assisted thoracoscopic lung biopsy is the currently preferred technique for diagnosing organizing pneumonia, because large lung specimens are necessary to make the diagnosis with confidence. Transbronchial lung biopsy may show organizing pneumonia but does not allow the exclusion of associated disorders. Corticosteroids are the current standard treatment of COP. Response to this treatment is generally impressive.

Keywords

Bronchiolitis obliterans, inflammatory lung disease, corticosteroids treatment

Name of disease

Cryptogenic organizing pneumonia (COP)

Synonym

Bronchiolitis obliterans organizing pneumonia (BOOP)

Definition

Organizing pneumonia corresponds to the presence of buds of granulation tissue (progressing from fibrin exudates to loose collagen embedding fibroblasts) in the lumen of the distal pulmonary airspaces [1]. The lesions predominate within the alveoli, but often

associated buds of granulation tissue are found in the bronchiolar lumen (bronchiolitis obliterans). This pathological pattern has no etiologic specificity, and may thus be encountered in a variety of inflammatory pulmonary disorders.

However, organizing pneumonia is the hallmark of the characteristic clinico-radiological entity of unknown cause called cryptogenic organizing pneumonia (COP). The latter terminology is currently preferred to the other name of this condition, i.e. idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP).

COP was recognized as a distinct disorder in the early 1980s after the reports of Davison *et al* [2] and Epler *et al* [3]. Further studies in the 1980s [4,5] described its characteristic features, and COP is now accepted as a rare but quite characteristic clinicopathologic entity in pulmonary medicine.

Differential diagnosis

The diagnosis of COP is based on both the typical pathological findings of organizing pneumonia and the lack of any identified cause.

Therefore, the following causes of organizing pneumonia must be carefully excluded before concluding that organizing pneumonia is cryptogenic.

Organizing pneumonia of determined cause

Infection is a common cause of organizing pneumonia (table 1). In bacterial infections, organizing pneumonia occurs mostly in nonresolving pneumonia where, despite control of the infectious organism by antibiotics, the inflammatory reaction remains active with further organisation of the intra-alveolar fibrinous exudate.

Table 1: Infectious causes of organizing pneumonia

Bacteria	<i>Chlamydia pneumoniae</i> <i>Coxiella burnetii</i> <i>Legionella pneumophila</i> <i>Mycoplasma pneumoniae</i> <i>Nocardia asteroides</i> <i>Pseudomonas aeruginosa</i> <i>Serratia marcescens</i> <i>Staphylococcus aureus</i> <i>Streptococcus group B</i> <i>Streptococcus pneumoniae</i>
Viruses	<i>Cytomegalovirus</i> <i>Herpes virus</i> <i>Human immunodeficiency virus</i> <i>Influenza virus</i> <i>Parainfluenza virus</i> <i>Human herpes virus-7</i>
Parasites	<i>Plasmodium vivax</i>

Fungi	<i>Cryptococcus neoformans</i> <i>Penicillium janthinellum</i> <i>Pneumocystis carinii (in AIDS)</i>
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Drugs are another cause of organizing pneumonia (table 2). Resolution of organizing pneumonia after stopping the drug is the best clue to establish causality.

A syndrome quite similar to cryptogenic organizing pneumonia has been identified recently in women with breast cancer receiving radiation therapy after surgery for a malignant tumor [6-13]. It is distinct from usual radiation pneumonitis, especially because pulmonary infiltrates occur or migrate outside the radiation fields and the response to corticosteroids is excellent without sequelae.

Table 2: Drugs identified as cause of organizing pneumonia

-	5-aminosalicylic acid ¹
-	Acebutolol
-	Acramin FWN
-	Amiodarone
-	Amphotericin
-	Bleomycin
-	Busulphan
-	Carbamazepine ²
-	Cephalosporin (cefradin)
-	Cocaine
-	Doxorubicin
-	Gold salts ³
-	Hexamethonium
-	Interferon alpha
-	Interferon alpha + cytosine arabinoside
-	Interferon + ribavirin
-	Interferon β1a
-	L-tryptophan
-	Mesalazine
-	Methotrexate
-	Minocycline
-	Nitrofurantoin
-	Nilutamide
-	Paraquat
-	Phenytoin
-	Sotalol
-	Sulfasalazine ¹
-	Tacrolimus
-	Ticlopidine
-	Transtuzumab
-	Vinbarbital-aprobarbital

¹In patients treated by this drug for ulcerative colitis or Crohn's disease which may themselves be associated with organizing pneumonia.

²In the course of lupus syndrome induced by the drug.

³In patients with rheumatoid arthritis which may itself be associated with organizing pneumonia.

Organizing pneumonia of unknown cause but occurring in a specific context [14]

The connective tissue disorders may be associated with organizing pneumonia. The idiopathic inflammatory myopathies may cause a characteristic organizing pneumonia syndrome.

Organizing pneumonia also occurs in rheumatoid arthritis and Sjögren's syndrome.

Pathological features of organizing pneumonia which may be present in Wegener's granulomatosis usually consist of small foci of organizing pneumonia at the periphery of otherwise typical granulomatous lesions.

It is well established that both lung transplantation and bone-marrow grafting may be complicated by constrictive mural bronchiolitis obliterans with airflow obstruction. Less commonly, organizing pneumonia occurs in transplanted lungs or after allogeneic bone marrow grafts.

Clinical description

Clinical characteristics [2,3,5,15-19]

Men and women are affected equally and are usually aged between 50 and 60 years. No predisposing factors have been identified.

The onset of symptoms is usually subacute with fever, nonproductive cough, malaise, anorexia and weight loss. Haemoptysis, bronchorrhea, chest pain, arthralgia and night sweats are uncommon. Dyspnea, usually mild, is occasionally severe in some acute and life-threatening cases. In most cases, symptoms develop over a few weeks (sometimes after a viral-like illness), and the diagnosis of COP is usually made after 6 to 10 weeks. At physical examination sparse crackles may be heard over affected areas.

Imaging [2-5,16,18,20-23]

The radiographic and computed tomography (CT) scan findings are characteristic in typical cases. They suggest the diagnosis when multiple patchy alveolar opacities with a peripheral and bilateral distribution are present. Their size ranges from a few centimetres to a whole lobe, their density varies from ground glass opacification to airspace consolidation with an air bronchogram. Other less common imaging patterns consist of either diffuse bilateral infiltration associating interstitial opacities and small superimposed alveolar opacities, or solitary focal lesions (often excised when lung cancer is suspected) which may correspond to unresolved pneumonia in some cases.

Lung function tests [5,21,24,25]

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. The transfer factor for carbon monoxide is reduced. Mild hypoxemia at rest and/or on exercise is common. Hypoxemia is occasionally severe.

Bronchoalveolar lavage and laboratory findings

Bronchoalveolar lavage is used in COP especially to exclude other disorders, or identify causes of COP and particularly infections. The differential white cell count may show a rather characteristic "mixed pattern" with increased lymphocytes (20-40%), neutrophils (about 10%), eosinophils and sometimes the presence of some plasma cells or mast cells [5,16,26].

There are no specific laboratory findings in COP. The erythrocyte sedimentation rate and C-reactive protein levels are increased and there is a moderate leucocytosis, with an increased proportion of neutrophils.

Diagnosis of cryptogenic organizing pneumonia

The diagnosis of COP relies on the association of typical pathological and clinico-radiological features, without any recognized cause or significant associated disorder. Pathological examination of lung biopsy specimens shows intra-alveolar buds of granulation tissue consisting of fibroblasts, myofibroblasts, and loose connective tissue. The buds may extend from one alveolus to the next, giving a rather characteristic "butterfly" pattern. Bronchiolar lesions consist of similar buds of granulation tissue inside the airway lumen in continuity with lesions in the alveoli [1, 27,28].

In COP the organizing pneumonia is the most conspicuous pathological feature and not just an accessory finding as seen in vasculitis, eosinophilic pneumonia, hypersensitivity pneumonitis, or nonspecific interstitial pneumonia. Furthermore, it is important to rule out any possible cause of organizing pneumonia, and especially infection using special stains.

Video-assisted thoracoscopic lung biopsy is the currently preferred technique for diagnosing organizing pneumonia, because large lung specimens are necessary to make the diagnosis with confidence. Transbronchial lung biopsy may show organizing pneumonia but does not allow the exclusion of associated disorders. Diagnosing organizing pneumonia by transbronchial biopsy is acceptable in quite typical cases, but careful follow-up is necessary in order to prompt a surgical biopsy if the evolution is unusual.

The diagnosis of COP seems to be increasingly made without biopsy in clinical practice. This may be risky since other disorders, like primary pulmonary lymphomas, may mimic COP.

Treatment and prognosis of organizing pneumonia

Although spontaneous improvement and slow improvement after prolonged treatment with

erythromycin have been reported, corticosteroids are the current standard treatment of COP [14,21,17,28]. The response to corticosteroids is generally remarkable. Clinical manifestations improve within 48 hours. Complete resolution of radiographic pulmonary infiltrates usually takes a few weeks.

In patients with typical COP we recommend a starting dose of about 0.75 mg/kg/day. After 2 to 4 weeks, the dose is gradually tapered. Relapses occur frequently as the dose of corticosteroids is reduced [29]. The final outcome is not significantly affected by the occurrence of relapses [29]. The duration of treatment is usually between 6 and 12 months, but some patients have successive relapses and require treatment for much longer.

The prognosis in typical COP is usually excellent when treated with corticosteroids [14,29,30].

However, there are reports of patients with severe and rapidly progressive COP [31,32]. Some cases with a poor outcome may represent an uncommon evolution of otherwise typical organizing pneumonia, but most are likely to be acute interstitial pneumonia or organizing acute respiratory distress syndrome (ARDS). Some patients with severe disease requiring assisted ventilation may improve completely with corticosteroids. Factors reported to be associated with a poor outcome in COP include a predominantly interstitial pattern on imaging, a lack of a lymphocytosis on the bronchoalveolar lavage (BAL) differential cell count, associated disorders [30], and a finding on histology of scarring and remodelling of the lung parenchyma in addition to organizing pneumonia [33].

Cytotoxic drugs, especially cyclophosphamide or azathioprine, have been occasionally used to treat COP [31, 34, 35], but they have not been evaluated. 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.

Pathogenesis of organizing pneumonia

Organizing pneumonia is the pathological hallmark of a distinct type of lung injury and repair rather than a disease with one defined etiology.

The process of intra-alveolar organization, which has been studied mainly in experimental animal models and in ARDS, results from a sequence of alveolar injury, intra-alveolar clotting with deposition of fibrin and subsequent colonisation by fibroblasts to produce a connective matrix (for review see ref. [36,37]). The injury to both capillary endothelial cells and alveolar epithelial cells allows the leakage of plasma proteins, especially coagulation factors, into the alveoli.

Alveolar damage is associated with both increased procoagulant activity and decreased fibrinolytic activity, which results in the intra-alveolar deposits of fibrin. 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 [38-40]) on fibroblasts, smooth muscle cells, and inflammatory cells. Elevated concentrations of macrophage inflammatory proteins MIP-1alpha and MIP-1beta were found in bronchoalveolar lavage fluid. They decreased after corticosteroid therapy accompanied by decreased lymphocytes, suggesting potential pathogenetic role [41].

How corticosteroids induce the disappearance of the well-organized fibrotic intra-alveolar buds is not known. Degradation of the connective matrix requires specific enzymes such as matrix metalloproteinases (MMP), gelatinases and stromelysins. Leucocytes and the fibroblasts themselves may produce these enzymes.

Conclusion and research perspectives

Although rare, COP is now a well-recognized entity, with characteristic clinical and radiological features, and pathological diagnostic criteria. Although corticosteroid treatment is very effective, we are not able to predict which patients will relapse after reducing or stopping treatment, nor do we know the most appropriate dose to start treatment and how long patients should be treated. Some patients are probably over treated 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 underlying this idiopathic persistent inflammatory and fibroproliferative process, which is dramatically responsive to corticosteroids.

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