

Update on cryptogenic organising pneumonia (idiopathic bronchiolitis obliterans organising pneumonia)

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Summary

Organising pneumonia, defined by intra-alveolar buds of connective tissue, may be a disorder secondary to a determined cause (infectious agents, drugs) or occurring in a specific context (as the connective tissue disorders). It may also be a cryptogenic interstitial pneumonia with charac-

teristic clinical and imaging features and especially an excellent response to corticosteroids.

Key words: organising pneumonia; bronchiolitis obliterans organising pneumonia; idiopathic interstitial pneumonias

Introduction

Organising pneumonia is characterised by the presence of buds of granulation tissue in the lumen of the distal pulmonary airspaces (alveoli and alveolar ducts) [1]. Buds of granulation tissue may also be present in the bronchiolar lumen (bronchiolitis obliterans). Although this pathological pattern may be encountered in a variety of inflammatory pulmonary disorders, it is the hallmark of the characteristic clinico-radiological entity of unknown

cause called cryptogenic organising pneumonia (COP), a terminology currently preferred to the other name of this condition, idiopathic bronchiolitis obliterans with organising pneumonia (BOOP).

COP was recognised as a distinct disorder with characteristic features in the 1980s [2–5], and is now accepted as a rare but quite characteristic clinicopathologic entity in pulmonary medicine.

Clinical description

Clinical manifestations [3–9]

Men and women are equally affected and are usually aged between 50 and 60 years.

The onset of symptoms (fever, nonproductive cough, malaise, anorexia and weight loss) is usually subacute. Haemoptysis, bronchorrhea, chest pain, arthralgia and night sweats are uncommon. Dyspnea is usually mild. Symptoms develop over a few weeks (sometimes after a viral-like illness). At physical examination sparse crackles may be present. The diagnosis of COP is usually made only after 6 to 10 weeks, especially after the patient does not improve with antibiotics given for a possible infectious pneumonia.

Imaging [2–6, 8, 10–13]

There are three main types of imaging profiles of COP.

The imaging features of COP are very char-

acteristic in typical cases, and thus strongly suggest the diagnosis when consisting of multiple patchy alveolar opacities with a peripheral and bilateral distribution. The size of the opacities varies from a few centimeters to a whole lobe, and their density from ground glass to consolidation with an air bronchogram.

Other less characteristic imaging patterns consist of either diffuse bilateral infiltrative opacities associating both interstitial opacities and small alveolar opacities, or solitary focal lesions diagnosed at pathological examination of specimen excised in the suspicion of lung carcinoma.

Lung function tests [3, 10, 11, 14]

Patients with COP usually have a mild or moderate restrictive ventilatory defect. Airflow obstruction may be present in smokers. The transfer factor for carbon monoxide is reduced. Mild

hypoxaemia at rest and/or on exercise is common. Hypoxaemia is occasionally severe but is not a characteristic feature of COP (in contrast with the usual airflow obstruction observed in patients with constrictive bronchiolitis especially after lung transplant or bone marrow graft).

Bronchoalveolar lavage and laboratory findings

Bronchoalveolar lavage helps especially to identify possible causes of organising pneumonia

and particularly infections (as *Pneumocystis carinii* pneumonia). The differential white cell count in COP may show a characteristic "mixed pattern" with increased lymphocytes (20–40%), neutrophils (about 10%), eosinophils and sometimes the presence of some plasma cells or mast cells [3, 8, 15].

The erythrocyte sedimentation rate and C-reactive protein level are increased, and there is a moderate leucocytosis at blood cell count, with an increased proportion of neutrophils.

Diagnosis of cryptogenic organising pneumonia

The diagnosis of COP requires both typical pathological and clinicoradiological features (allowing the diagnosis of organising pneumonia), and the lack of any recognised cause or significant associated disorder.

Lung biopsy specimens show intra-alveolar buds of granulation tissue consisting of fibroblasts, myofibroblasts, and loose connective tissue. Bronchiolar lesions (when present) consist of similar buds of granulation tissue inside the airway lumen [1, 16, 17]. Organising pneumonia is the most conspicuous pathological feature in COP, and not just a minor associated lesion as seen in other conditions like vasculitis (especially Wegener's granulomatosis), eosinophilic pneumonia, hypersensitivity pneumonitis, or nonspecific interstitial pneumonia. Careful examination is necessary to rule

out any possible cause of organising pneumonia (and especially infection using special stains).

Video-assisted thoracoscopic lung biopsy is now the best technique for obtaining the large lung specimens necessary to make the diagnosis of COP with confidence. Transbronchial lung biopsy may show organising pneumonia but does not allow the exclusion of associated disorders. Diagnosing organising 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 under treatment 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 on imaging.

Differential diagnosis of cryptogenic organising pneumonia

Table 1

Infectious causes of organising pneumonia (adapted from reference [21]).

| |
|---------------------------------------|
| 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 pneumoniae</i> |
| Viruses |
| Herpes virus |
| Human immunodeficiency virus |
| Influenza virus |
| Parainfluenza virus |
| Parasites |
| <i>Plasmodium vivax</i> |
| Fungi |
| <i>Cryptococcus neoformans</i> |
| <i>Penicillium janthinellum</i> |
| <i>Pneumocystis carinii</i> (in AIDS) |

Once the diagnosis is proven histopathologically, organising pneumonia is further called cryptogenic only in cases where no determined cause is found, and where no specific context is present in association with organising pneumonia.

Organising pneumonia of determined cause

Several types of infection may cause organising pneumonia (table 1), when the inflammatory process remains active with further organisation of the intra-alveolar fibrinous exudate, despite control of the infectious organism by antibiotics.

Drugs may also cause organising pneumonia (table 2). Resolution of organising pneumonia typically occurs after stopping the drug.

A syndrome quite similar to cryptogenic organising pneumonia may develop in women receiving radiation therapy to the breast for cancer [18–20]. In contrast with usual radiation pneumonitis, pulmonary infiltrates occur or migrate outside of the radiation field and regress with corticosteroids without sequelae.

Table 2

Drugs identified as cause of organising pneumonia (adapted from reference [21]).

| |
|-----------------------|
| 5-aminosalicylic acid |
| Acebutolol |
| Acramin FWN |
| Amiodarone |
| Amphotericine |
| Bleomycin |
| Busulphan |
| Carbamazepine |
| Cocaine |
| Fluoxetine |
| Gold salts |
| Interferon alpha |
| Interferon beta-1a |
| L-tryptophan |
| Mesalazine |
| Minocycline |
| Nilutamide |
| Paraquat |
| Phenytoin |
| Sotalol |
| Sulfasalazine |
| Ticlopidine |

Organising pneumonia of unknown cause occurring in a specific context [21]

Organising pneumonia may occur in association with inflammatory and/or systemic disorders, especially the connective tissue disorders as the idiopathic inflammatory myopathies syndrome. Organising pneumonia also occurs in rheumatoid arthritis and Sjögren's syndrome.

Disorders mimicking organising pneumonia

The main disorders resembling the typical imaging features of COP (patchy alveolar opacities with air bronchogram) consist mainly of the low grade pulmonary lymphomas and bronchioloalveolar carcinoma. These must be carefully excluded, especially primary pulmonary lymphomas which may initially markedly improve with corticosteroid treatment.

Treatment of organising pneumonia

Corticosteroids are the current standard treatment of COP [9, 11, 21], although spontaneous improvement and slow improvement after prolonged treatment with erythromycin have been reported. Clinical manifestations improve within 48 hours with corticosteroids. Radiographic pulmonary infiltrates usually disappear within a few weeks.

In patients with typical COP we start with a 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 or after stopping treatment [22]. The final outcome is not significantly affected by the occurrence of relapses [22]. 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 excellent in the vast majority of patients treated with corticosteroids [21–23].

Patients with severe and rapidly progressive

COP have been occasionally reported [24, 25]. Such cases may more likely represent acute interstitial pneumonia or organising 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, lack of lymphocytosis at BAL differential cell count, associated disorders [23], and a finding on histology of scarring and remodelling of the lung parenchyma in addition to organising pneumonia [26].

Cytotoxic drugs (cyclophosphamide, azathioprine), occasionally used to treat COP [24, 27, 28], have not been evaluated. Cyclophosphamide may be used only exceptionally in severely ill patients who do not improve with corticosteroid treatment within a few days and in patients who fail to improve despite a prolonged course of corticosteroids.

Conclusion

COP is now a rare but well-recognised entity, with characteristic clinical and radiological features and pathological diagnostic criteria.

Whether the cause of COP is unique or whether it is the common inflammatory denominator of several distinct triggers is not known.

Corticosteroid treatment is very effective, but the dose and length of treatment have not been clearly established. Some patients are probably overtreated whereas others would benefit from longer treatment.

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