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What you need to know about: organising pneumonia

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Abstract

Organising pneumonia was first described in the context of respiratory infection, but over time has become established as its own entity. It is an area of diagnostic complexity because of the non-specific presenting symptoms and signs that can often mimic other respiratory pathology. Multidisciplinary review to correlate clinical, radiological and histopathological features can aid timely and effective diagnosis. This article discusses the epidemiology, aetiology, clinical, radiological and histopathological features, investigation and management of organising pneumonia.

Key words: COVID-19 pneumonitis; Idiopathic interstitial pneumonias; Masson bodies; Multidisciplinary team discussion; Organising pneumonia

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Introduction

Organising pneumonia, formerly known as bronchiolitis obliterans with organising pneumonia, has seen great progress in understanding since its description in 1983. For years it was described in the context of respiratory infection, but eventually became established as its own entity: cryptogenic organising pneumonia. As a proportion of cases are secondary to other pathologies, it has been suggested that the term 'organising pneumonia' should be used with modifiers, such as organising pneumonia associated with rheumatoid arthritis (Travis et al, 2013).

Organising pneumonia is a non-specific inflammatory and tissue repair process that resembles pneumonia, but is not the direct result of infection. It is characterised by the formation of organised buds of granulation tissue (Masson bodies), obstructing the alveolar lumen and bronchioles, resulting in respiratory failure.

The European Respiratory Society and American Thoracic Society compiled a diagnostic framework to aid the classification of idiopathic interstitial pneumonias (Travis et al, 2013). This moved away from a classification based solely on histopathology to an integrated framework based on key clinical, radiological and histopathological findings.

Epidemiology

Men and women tend to be affected equally. The mean age at presentation is 50–60 years old. Non-smokers or ex-smokers are affected twice as much as smokers (Mehrjardi et al, 2017).

Classification and aetiology

Organising pneumonia can be separated into two categories: cryptogenic organising pneumonia and secondary organising pneumonia. Although cryptogenic organising pneumonia differs from secondary organising pneumonia, they have similar treatment responses, relapse rates and mortality (Drakopanagiotakis et al, 2011). Differentiation allows treatment of the underlying aetiology, which may improve prognosis. Possible aetiologies of secondary organising pneumonia are summarised in Table 1.

Clinical features

Patients present sub-acutely with cough, exertional dyspnoea and constitutional symptoms (Drakopanagiotakis et al, 2011). Symptoms can vary according to underlying aetiologies

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Table 1. The aetiology of organising pneumonia secondary to lung injury

Cause		Details
Infection	Bacteria	*Streptococcus pneumoniae,* atypical pneumonias, atypical Mycobacterium, *Staphylococcus aureus, Pseudomonas aeruginosa*
	Virus	HIV, influenza, parainfluenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
	Parasite	*Plasmodium vivax*
	Fungal	*Cryptococcus neoformans, Pneumocystis jirovecii*
Toxins	Drug toxicity	Nitrofurantoin, carbamazepine, amiodarone, chemotherapy agents such as bleomycin, immune checkpoint inhibitors
	Inhaled toxins	Cocaine, industrial gases, ammonia
	Radiotherapy	For example, at target site
Rheumatological disorders	Granulomatosis with polyangiitis	
	Connective tissue disorders	Polymyositis or dermatomyositis
Transplant	Bone marrow transplant	
	Lung transplant	
Other diseases	Micro-aspiration	Gastro-oesophageal reflux
	Malignancy	Pulmonary lymphoma and lung cancer
	Idiopathic non-specific interstitial pneumonia and eosinophilic pneumonia	
	Pulmonary infarct	

(Cordier, 2006). On examination, coarse crackles and rales may be auscultated. Examination may also be normal.

Radiographic features

Chest X-ray features

Consolidation is the most common finding and can be unilateral, bilateral and often migratory. The inflammatory process tends to favour peripheral, subpleural and peri-bronchial areas.

Extrapulmonary findings are uncommon, but can include small pleural effusions (Roberton and Hansell, 2011). Areas of granulation can appear as small nodules (<1 cm) and be numerous in immunocompromised individuals.

High resolution computed tomography features

There are three types of high resolution computed tomography findings that are characteristic of the imaging subtypes of cryptogenic organising pneumonia (Cordier, 2006).

Typical cryptogenic organising pneumonia: multiple alveolar opacities

Multiple alveolar opacities that are peripheral, bilateral and spontaneously migrate and regress are seen in ~75% of patients (Roberton and Hansell, 2011) (Figure 1). Their density can vary from ground glass (present in 80–95% of patients) to overt consolidation (present in 60–90% of patients) (Mehrjardi et al, 2017).

Focal cryptogenic organising pneumonia: solitary opacities

Solitary opacities or multiple small nodules seen bilaterally can be solid or cavitating and are often observed in immunocompromised individuals (Mehrjardi et al, 2017) (Figure 2). Distinguishing them from lung cancers is difficult, so lesions are often excised, with the diagnosis subsequently proved on histology.

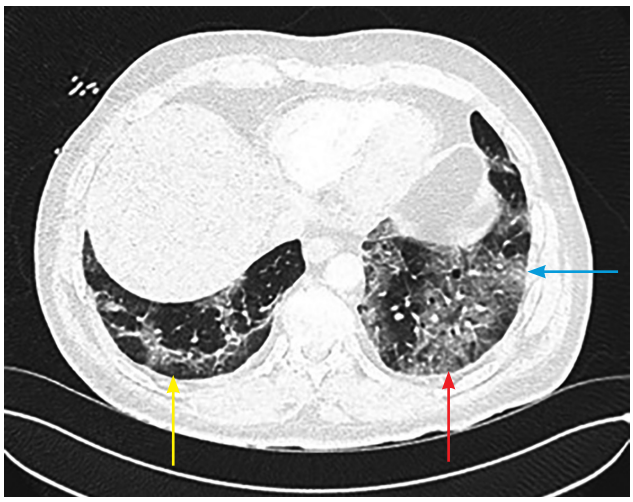

Figure 1. Computed tomography image demonstrating multiple alveolar opacities associated with consolidation (blue arrow), ground-glass change (red arrow) and perilobular abnormalities (yellow arrow).

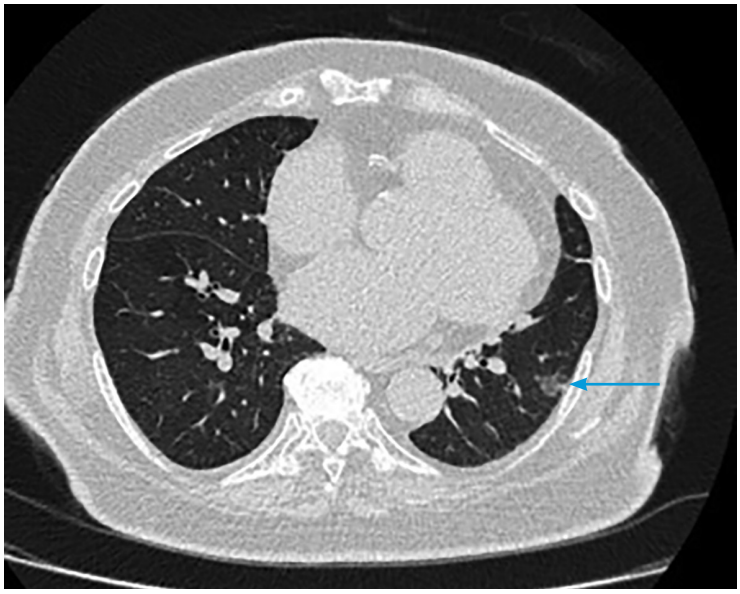

Figure 2. Computed tomography image demonstrating a solitary ground-glass nodule (blue arrow).

Infiltrative cryptogenic organising pneumonia: infiltrative opacities

Interstitial and superimposed alveolar opacities forming a polymorphic pattern follow a perilobar distribution (Figure 3). This is usually associated with consolidation and presents with diffuse bilateral infiltration, but can present unilaterally.

Other signs associated with organising pneumonia

Peri-lobular abnormalities

These are curved bands of consolidation, with blurred borders, abutting the pleural surface and surrounded by aerated lung (Cordier, 2006). In one study, 56% of patients had peri-lobular abnormalities on high resolution computed tomography, suggesting that this is a characteristic sign (Ujita et al, 2004) (Figure 1).

Atoll sign

Also known as the reverse halo sign, this is an area of ground glass change that is surrounded by dense, crescent-shaped consolidation (Figure 4). The ground glass change corresponds to alveolar inflammation, while the crescentic consolidation represents granulation tissue within distal airspaces (Voloudaki et al, 1996).

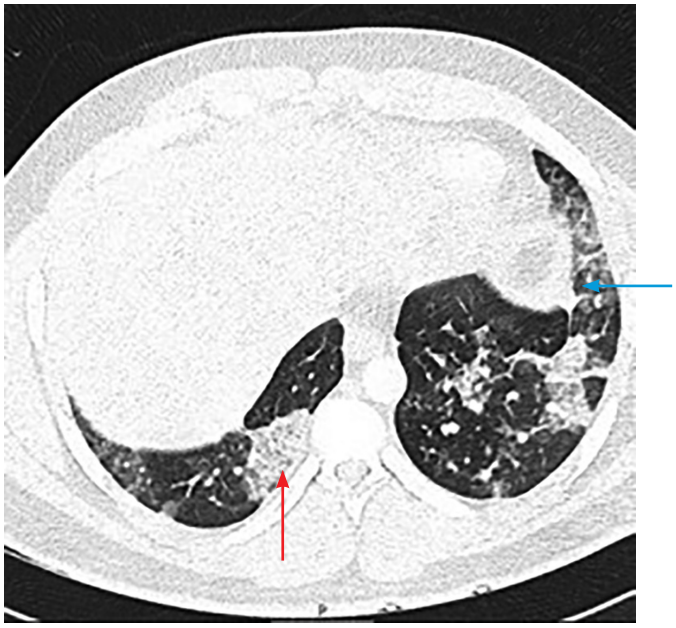

Figure 3. Computed tomography image demonstrating organised inflammatory infiltrates (blue arrow) and consolidations (red arrow).

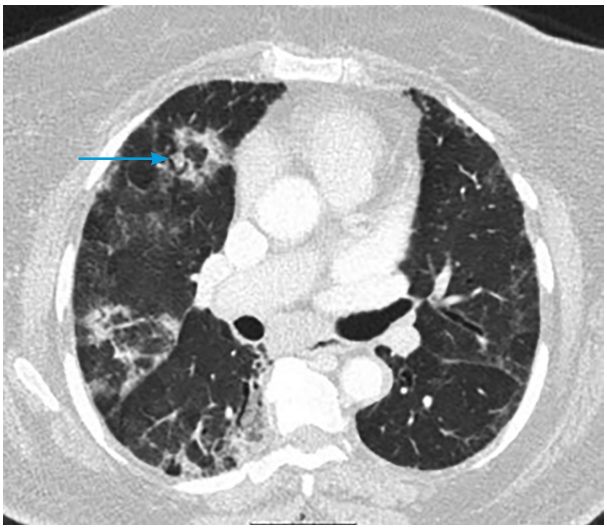

Figure 4. Computed tomography image demonstrating the reverse halo sign (blue arrow).

Parenchymal bands

Thick parenchymal bands extend from the visceral pleura along the tract of a bronchus towards the pleura (Mehrjardi et al, 2017). They are usually up to 5 cm long and 1–3 mm thick.

Diagnostic work-up

It is essential that a thorough clinical and drug history is conducted to identify offending agents that could cause secondary organising pneumonia, particularly as patients could be counselled on medications to cease or avoid. Possible causative agents are summarised in Table 2.

Laboratory-based investigations should include relevant serological tests to screen for common conditions associated with organising pneumonia, such as HIV antibodies, autoimmune or connective tissue diseases.

In most cases, the clinical, laboratory and radiological findings are enough to diagnose organising pneumonia and start treatment following discussion within the multidisciplinary team (Travis et al, 2013; Ryerson et al, 2017). For other cases, re-discussion within the multidisciplinary team and lung biopsy is recommended.

Lung biopsy and histopathology findings

Transbronchial biopsy can obtain tissue, but is frequently inadequate given the small samples obtained and loss of architecture from crush artefact. Video-assisted thoracoscopic surgery biopsy permits the retrieval of larger tissue sections and sampling of multiple lobes. However, not all patients will be suitable candidates as a result of frailty, hypoxaemia or comorbidities. Such cases should be discussed within the multidisciplinary team and the decision to treat should be based upon clinical and radiological features, balanced alongside the risks and benefits of treatment.

Organising pneumonia is defined histopathologically by 'buds of granulation tissue in distal air spaces, progressing from fibrin exudates to loose collagen-containing fibroblasts' (Cordier, 2000). However, this is not specific to organising pneumonia, so histology alone cannot confirm diagnosis. Four histopathological stages have been described in the development of organising pneumonia (Table 3).

Other diagnostic tests

Bronchoalveolar lavage

Bronchoalveolar lavage cellular analysis in patients with interstitial lung disease allows the clinician to narrow down the differential diagnosis in those presenting with non-specific findings (Meyer et al, 2012). A lymphocyte differential count >25% is suggestive, but not specific, for cryptogenic organising pneumonia. A normal bronchoalveolar lavage cell differential diagnosis does not exclude a diagnosis of interstitial lung disease, nor can bronchoalveolar lavage diagnose interstitial lung disease subtypes or provide prognostication.

Lung function tests

A mild to moderate restrictive pattern is the most common abnormality (Cordier, 2006). Patients may have a reduced transfer factor proportionate to their restrictive deficit. However, in many, lung function is normal and may provide little information.

Management

Spontaneous resolution is possible in cryptogenic organising pneumonia, but the mainstay of management is corticosteroids. Clinical response is rapid, with symptom improvement

Table 2. Drug toxicity associated with organising pneumonia

Classes	Drugs
Antibiotics	Nitrofurantion
Chemotherapy agents	Bleomycin, oxaliplatin-combined chemotherapy
Anti-epileptic drugs	Carbamazepine, lamotrigine
Anti-arrhythmics	Amiodarone, beta-blockers
Immunotherapy	Pembrolizumab, immune checkpoint inhibitors, rituximab

Table 3. Histopathological stages in development of organising pneumonia

Stage	Process	Details
1	Leakage	Alveolar epithelial damage causes pneumocyte death, resulting in gaps within the basal lamina. Proteins and inflammatory cells leak into airspace
2	Coagulation	Activation of the clotting cascade leads to fibrin deposition.
3	Organisation	Organisation leads to the development of intra-alveolar fibro-inflammatory buds. Fibroblasts multiply, inhabit the alveolar and undergo further change resulting in an intra-alveolar matrix (Masson bodies)
4	Resorption	Receding of the inflammatory component results in resorption of the matrix. The loose matrix is susceptible to breakdown and the lung architecture is preserved, so the process can be reversed with treatment

From Roberton and Hansell (2011)

within 48 hours and marked improvement after 7 days (Cordier, 2000). However, radiological appearances can take months to resolve.

While the efficacy of corticosteroids is well established, dosing recommendations and treatment duration vary. A suggested starting dose is 0.5–1.5 mg/kg/day (Cordier, 2006). In severe cases, methylprednisolone is recommended, but should be administered under specialist guidance.

Proposed treatment duration is 6 months to 1 year; however, because of side effects, patients are usually weaned sooner than the recommended 6–12 months if symptoms and radiological features resolve. Weaning should be balanced against the risk of relapse. One suggested protocol starts with a dose of 0.75 mg/kg/day for 4 weeks, 0.5 mg/kg/day for 4 weeks, 20 mg for 4 weeks, 10 mg for 6 weeks, 5 mg for 6 weeks and stopping (Lazor et al, 2000).

Relapse rates have been reported as 13–58% and can occur at the original site or new locations (Lazor et al, 2000). Predictors of relapse include delayed treatment and deranged liver function. While relapse is common, it is not associated with increased mortality or morbidity, so some may choose to accept the risk of relapse than tolerate lengthy treatment (Lazor et al, 2000; Zhou et al, 2019).

Occasionally, immunosuppressive agents such as cyclophosphamide and azathioprine are used for difficult-to-manage cases (Cordier, 2000). However, there are few data to support this and it should only be considered in specialist centres following multidisciplinary team discussion.

One study described a case where azithromycin was used to treat mild cryptogenic organising pneumonia (Ding et al, 2015). A subsequent literature review found that, of 29 patients receiving single-agent macrolide therapy, 80% were disease-free within 3–14 months, while 20% showed no improvement after a month and required switching to single-agent or combination glucocorticoid therapy. Although a small sample size, this suggests that macrolide therapy may emerge as a treatment for mild cryptogenic organising pneumonia.

SARS-CoV-2 and organising pneumonia

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that caused the COVID-19 pandemic. The most common symptoms were fever, dry cough and fatigue (World Health Organisation, 2021). Those with more severe illness experienced hypoxia.

Features of an organising pneumonia-pattern of lung injury remain the most common finding and are described in virtually all cases (Kory and Kanne, 2020). Computed tomography findings correlate with four distinct disease phases: early onset (0–4 days), progressive (5–8 days), peak (9–13 days) and absorption (>14 days) (Pan et al, 2020). Initially there are ground-glass opacities, usually with a sub-pleural or peripheral distribution (Hani et al, 2020), with a crazy-paving pattern (mixed-in areas of consolidation and/or reticular changes), which transform into multifocal consolidation, then linear consolidation and, eventually, into changes seen in organising pneumonia. In most patients, there is multi-lobar involvement

Numerous studies reported COVID-19 as being steroid responsive and the RECOVERY trial led to the approval of the use of dexamethasone. However, given the high prevalence of organising pneumonia in patients with COVID-19, dexamethasone 6 mg once daily for 10 days may not be sufficient, as secondary organising pneumonia often requires higher doses for longer periods (Kory and Kanne, 2020). Further studies are required to determine optimum dosage and treatment duration.

Acute fibrinous and organising pneumonia

Acute fibrinous and organising pneumonia is a rare idiopathic interstitial pneumonia with a clinical course that lies on a spectrum between organising pneumonia and diffuse alveolar damage (Travis et al, 2013). It can be idiopathic or associated with connective tissue disease, toxins or other respiratory diseases.

Key points

- Organising pneumonia is a non-specific inflammatory process within the respiratory system that is not the result of infection, but does resemble pneumonia.
- The aetiology is divided into cryptogenic organising pneumonia and secondary organising pneumonia.
- Diagnosis requires correlation of symptoms with specific histological and radiological findings.
- Patients should be treated with high-dose steroids and other forms of immunosuppression can potentially be considered.
- Organising pneumonia should be considered in patients being treated for respiratory infection who are not responding to antibiotic therapy.

It is histologically characterised by fibrin balls and Masson bodies within the alveoli and inflammatory cells within the interstitium. It does not meet the criteria for either organising pneumonia or diffuse alveolar damage (Mehrjardi et al, 2017).

Acute fibrinous and organising pneumonia is a distinct histopathological condition with no characteristic radiological findings. Therefore, it is important to exclude conditions with similar appearances, including disseminated malignancy and tuberculosis. However, its clinical course and radiological findings do correlate well. Those with rapidly progressive disease have similar radiological findings to those of diffuse alveolar damage (diffuse, dependent consolidation and ground-glass changes), while those with a protracted course display findings consistent with organising pneumonia. Corticosteroids remain the first-line treatment for acute fibrinous and organising pneumonia (Kory and Kanne, 2020).

Uncertainties

While there are some key features within organising pneumonia, it is not fully understood and can present atypically. If areas of non-specific consolidation or nodular lesions are seen on imaging, then malignancy and infection should be excluded. However, if several specific features are found together, or lesions are waxing and waning, then organising pneumonia should be suspected (Baque-Juston et al, 2014).

Prognosis

Prognosis in typical organising pneumonia is good and the majority of patients recover completely. Factors associated with poor prognosis include a ‘predominantly interstitial pattern’ on imaging, normal or low lymphocyte count on bronchoalveolar lavage, secondary organising pneumonia and those who develop respiratory failure requiring ventilatory support.

Conclusions

Organising pneumonia is a complex but established pathological process. Multidisciplinary review of symptoms alongside characteristic radiology and histology can streamline diagnosis and aid timely treatment. However, as a result of the significant side-effect profile of steroid therapy, more data are required to evaluate the optimal dosing regimens and the use of steroid-sparing agents.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Curriculum checklist

This article addresses the following requirements from the general internal medicine curriculum:

- Managing an acute specialty-related take
- Providing continuity of care to medical inpatients
- Managing a multidisciplinary team.

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