Review

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Current approaches in the diagnosis and treatment of organizing pneumonia

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ABSTRACT

Organizing pneumonia (OP), is a rare yet well-defined form of interstitial lung disease. The condition can be idiopathic, termed cryptogenic organizing pneumonia (COP), or secondary to various causes, including infections, connective tissue diseases, medications, and malignancies. OP typically presents with nonspecific symptoms such as cough, dyspnea, fever, and weight loss, often mimicking other respiratory conditions like pneumonia or interstitial lung diseases. Radiological findings are varied but commonly include bilateral, patchy consolidations or ground-glass opacities with preserved lung volumes. Diagnosis often requires high-resolution computed tomography (HRCT) and may be confirmed by lung biopsy when clinical and imaging findings are inconclusive. Laboratory studies and bronchoalveolar lavage can aid in excluding alternative diagnoses. Glucocorticoids remain the mainstay of treatment, with most patients responding well to therapy. This review explores current advances in the diagnosis, differential diagnosis, and management of OP, emphasizing the importance of a multidisciplinary approach to optimize patient outcomes.

Keywords: Organizing pneumonia, cryptogenic organizing pneumonia, interstitial lung disease, glucocorticoid therapy

INTRODUCTION

Organizing pneumonia (OP) is a rare yet highly distinctive form of interstitial lung disease. Previously known as bronchiolitis obliterans organizing pneumonia (BOOP), this condition was reclassified as OP in the guidelines updated by the American Thoracic Society/European Respiratory Society (ATS/ERS) on the classification of idiopathic interstitial pneumonias. When no underlying cause is identified, it is referred to as "idiopathic/cryptogenic" organizing pneumonia (COP). If it develops secondary to connective tissue diseases, various medications, malignancies, or other interstitial pneumonias, it is termed secondary OP. The causes of Secondary OP are listed in **Table 1**. It is an interstitial lung disease that typically involves recurrent involvement of the peripheral areas of the lung, resulting from destruction of the alveolar wall, and is characterized by a good response to systemic glucocorticoid therapy.

Table 1. Causes of secondary organizing pneumonia

Systemic diseases	Conditions such as *Crohn's disease, ulcerative colitis, Behçet's disease, systemic lupus erythematosus, scleroderma, myelodysplastic syndromes, leukemia,* and malignancies.
Collagen tissue diseases	*Rheumatoid arthritis, Sjögren's syndrome, Wegener's granulomatosis.*
Infectious agents	*Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, Pseudomonas aeruginosa, Streptococcus pneumoniae,* viruses (*Herpes, HIV, Influenza, Parainfluenza*), *Pneumocystis jirovecii,* and others.
Drugs	Medications such as *aminosalicylic acid, amiodarone, bleomycin, cocaine, sulfasalazine, mesalazine, gold salts, phenytoin, ticlopidine,* among others.
Radiotherapy	

EPIDEMIOLOGY

While OP can affect individuals of any age, it is more commonly observed in the fifth and sixth decades of life. The disease occurs with similar frequency in both men and women.[1] Precise data on its incidence are not available; however, it is recognized as a rare condition.

PATHOGENESIS

The exact pathogenesis of cryptogenic organizing pneumonia (COP) remains unclear. Following acute damage to the alveolar epithelium, plasma proteins and fibroblasts accumulate within the alveolar lumen, leading to fibrin deposition. This

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is followed by a reversible inflammatory and fibroproliferative process, characterized by fibroinflammatory buds (Masson bodies) that do not disrupt the lung's architecture.

Some studies suggest that COP may be associated with the abnormal regulation of vascular endothelial growth factor and matrix metalloproteinases.[2,3] Additionally, publications propose a relationship between microaspiration caused by gastroesophageal reflux and COP.[4] Environmental factors have also been reported to play a role in its development.[5]

CLINICAL FEATURES

The clinical presentation is highly characteristic. The most common symptoms include non-productive cough, dyspnea, weight loss, fever, and fatigue, often accompanied by a viral infection-like syndrome that began a few weeks earlier. These symptoms are frequently observed in patients with unresolved or recurrent pulmonary infiltrates, mimicking infectious pneumonia. As a result, it is often initially evaluated as community-acquired pneumonia but should be considered when there is insufficient response to empirical antibiotic therapy. Similar to interstitial lung diseases (ILDs), symptoms or history suggestive of connective tissue diseases-such as arthralgias, dry eyes, dry mouth, or muscle weakness-may also be present. A history of medication use, therapeutic radiation, or exposure to smoke or dust should be investigated, especially in cases of secondary OP. Additionally, a recent study evaluated the seasonal characteristics of COP and reported that the highest rates of diagnosis and hospitalization occurred during the spring season.[6]

PHYSICAL EXAMINATION FINDINGS

Inspiratory crackles are heard in approximately 60% of patients with COP. Fewer than 5% of cases present with finger clubbing. Additionally, systemic examination findings such as alopecia, Gottron's papules, or heliotrope rash should be noted, particularly given the associations with dermatomyositis, polymyositis, and scleroderma.

RADIOLOGICAL FINDINGS

The radiological findings of COP are variable and are presented in **Table 2**. Typically, bilateral, diffuse, patchy consolidation or ground-glass opacities are observed, with no changes in lung volumes. Consolidations may also exhibit recurrent and migratory characteristics.

Table 2. Radiological findings of cryptogenic organizing pneumonia[7]

- Bilateral, diffuse, patchy consolidation or ground-glass opacities with unchanged lung volumes
- Opacities often localized to peripheral lung fields, similar to chronic eosinophilic pneumonia
-Recurrent or shifting lung opacities
-Unilateral consolidation or ground-glass opacities
-Nodular opacities
-Minimal and usually unilateral pleural effusion (5%)

LABORATORY FINDINGS

There are no specific laboratory findings for COP.[8] Patients frequently present with clinical features resembling pneumonia; therefore, routine laboratory tests should include complete blood count, blood urea nitrogen, creatinine, and hepatic function tests. Leukocytosis is present in approximately 50% of patients.[9] While not routinely utilized, elevated erythrocyte sedimentation rate (ESR; often ≥100 mm/hr) and C-reactive protein are found in 70-80% of patients. For patients hospitalized with suspected community-acquired pneumonia, additional tests may be performed to identify pathogens, such as sputum Gram staining and culture, or testing for pneumococcal and Legionella antigens.

COP patients may develop mild to moderate restrictive pulmonary function abnormalities. Most patients exhibit reduced carbon monoxide diffusion capacity. Mild hypoxemia, either at rest or during exercise, is a common finding observed in approximately 80% of cases.

HISTOPATHOLOGICAL FINDINGS

In COP, histopathological examination reveals granulation tissue buds (Masson bodies) composed of fibroblasts, collagen, and fibrinous exudates within alveolar ducts and alveoli. Two main criteria must be met to establish the histopathological diagnosis of COP:

1.The sample must exhibit the characteristic histopathological features of OP.

2.There should be no histopathological features indicative of other processes, such as:

- Granulomas suggestive of hypersensitivity pneumonitis.
- Prominent eosinophilia suggestive of chronic eosinophilic pneumonia.
- Temporal heterogeneity of lesions or fibroblast foci characteristic of usual interstitial pneumonia.

To ensure adequate tissue is obtained for diagnosis and to exclude other processes like nonspecific or usual interstitial pneumonia, transthoracic biopsy under CT guidance or video-assisted thoracoscopic surgery (VATS) is recommended instead of transbronchial biopsy.

DIAGNOSIS

Patients with COP often present with symptoms suggestive of community-acquired pneumonia. Less commonly, they may present with clinical and radiographic features similar to other interstitial lung diseases (ILDs). The hallmark features in these patients include subacute cough and dyspnea, with peripheral, irregularly defined ground-glass infiltrations or consolidations that do not respond to antibiotic treatment.

High-resolution computed tomography (HRCT) is used to evaluate the extent of lung involvement and differentiate COP from other ILDs.

Spirometry is used to evaluate diffusion capacity, determine disease severity, and monitor disease.

OP may present as an initial clinical manifestation of dermatomyositis and polymyositis. Less frequently, it may be associated with rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. In patients without overt symptoms of rheumatologic diseases, it is recommended to test for antinuclear antibody, rheumatoid factor, creatine

kinase, antitopoisomerase (anti-Scl70), anticentromere antibody, anti-double-stranded DNA, and anti-JO1.

Bronchoalveolar lavage (BAL) typically demonstrates a mixed pattern, with lymphocytes (20-50%) being predominant, and neutrophils (5-10%) and eosinophils (5-25%) also elevated.[10] While BAL is not diagnostic for OP, it is essential for ruling out alternative diagnoses.

In cases where COP diagnosis remains uncertain or to exclude other potential diagnoses, transthoracic lung biopsy under CT guidance is recommended. If the disease does not regress as expected with treatment, larger tissue samples should be obtained through video-assisted thoracoscopic surgery (VATS) or thoracotomy. In most cases, the differential diagnosis includes atypical infections, eosinophilic pneumonia, alveolar hemorrhage, or lymphangitic malignancy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of COP includes a wide range of diseases with similar clinical, radiological, and histopathological features:

Pneumonia

The onset of symptoms and radiographic appearance often mimic community-acquired pneumonia; however, COP is differentiated by the prolonged duration of symptoms and lack of response to antibiotic therapy.

Chronic Eosinophilic Pneumonia (CEP)

CEP can present with clinical features similar to COP. Both diseases show subpleural patchy consolidation areas. Peripheral eosinophilia and eosinophil counts exceeding 25% in bronchoalveolar lavage (BAL) favor CEP. Response to treatment is typically slower in COP, while CEP often shows a rapid response to corticosteroids within a few days.

Hypersensitivity Pneumonitis (HP)

The clinical presentation of COP (e.g., cough, dyspnea, fatigue, weakness, loss of appetite, and weight loss) is similar to subacute HP. However, subacute HP is distinguished by its radiographic findings (e.g., widespread micronodules and ground-glass appearance) and a history of exposure to an etiological agent. Additionally, BAL findings in HP typically reveal a higher percentage of lymphocytes, which supports the diagnosis of HP.

Pulmonary Lymphoma

The radiological appearance of pulmonary lymphoma, including areas of consolidation and air bronchograms, can resemble COP. However, in lymphoma, consolidation is typically unilateral, focal, and not widespread.

Pulmonary Lymphomatoid Granulomatosis (PLG)

PLG is a type of lymphoproliferative disease that can mimic multifocal COP. On CT imaging, PLG often presents with multiple irregularly defined nodules. Lung biopsy reveals polymorphic lymphoid infiltrates, transmural infiltration of arteries and veins by lymphoid cells (angiitis), and focal necrotic areas within the lymphoid infiltrates.

Diffuse Alveolar Damage (DAD)

Diffuse alveolar damage is the most common finding in patients with acute respiratory distress syndrome (ARDS). It represents a nonspecific histopathological reaction to lung injury. Rarely, some cases of COP may exhibit a fulminant onset and rapidly progress to respiratory failure.[11]

TREATMENT

The treatment of COP has not been extensively studied in randomized trials. Consequently, treatment decisions are based on observations from case series and clinical experience.[12] The decision to initiate treatment and the choice of the initial therapy depend on factors such as the severity of symptoms, baseline lung function, the extent of radiographic involvement, and the rate of disease progression.[11]

Patients with Minimal Radiological Findings and Symptoms

For patients with mild symptoms and minimal radiological involvement, follow-up without treatment is recommended unless symptoms or lung function show any signs of worsening. Regular follow-up every 8-12 weeks is advised to monitor symptoms and pulmonary function. Spontaneous remission is rare (<10%) but can occur in mild cases.

In patients with mild radiological findings but significant symptoms, macrolides may be considered if glucocorticoids cannot be administered. The benefits of macrolide therapy are likely linked to their anti-inflammatory effects. If symptoms do not improve despite radiological stability during macrolide treatment, the therapy duration can be extended.[13]

Case reports have described favorable responses to macrolide antibiotics in patients with mild symptoms, such as:

- **Clarithromycin:** 250–500 mg twice daily.
- **Azithromycin:** 250 mg daily or 500 mg three times per week.[14]

These treatments often require a prolonged duration of 3-6 months. Reducing the macrolide dose to once daily has been successful in some patients but has also been associated with recurrences in others.

Patients with Symptoms but Without Severe Respiratory Failure

Most patients with COP have progressive symptoms and pulmonary function test abnormalities with widespread radiographic changes. Treatment with oral glucocorticoids is recommended in these patients. In general, it is recommended to start with prednisone at a dose of 0.5-1 mg/kg/day, depending on ideal body weight, and increase to a maximum of 60 mg/day. In patients with relative contraindications to glucocorticoid therapy, azathioprine or mycophenolate mofetil is recommended, preferably in combination with a lower dose of prednisone. Many patients begin to show a clinical response within the first few days of glucocorticoid therapy, but significant response is usually seen after a few weeks. Radiological findings usually resolve within 3-4 months.

If there is a response after four to six weeks from the start of treatment, the dose should be gradually reduced to 0.25 mg/kg/day over 2 to 4 weeks. It is recommended to continue at this dose for 4 to 6 months. After four to six months of oral prednisone, if the patient remains stable or improves, it should be tapered off gradually over the next six weeks. In patients who respond rapidly to systemic glucocorticoids, the dose should be increased to 0.25 mg/kg and then tapered off gradually over three to four months.[15]

Pneumocystis jirovecii prophylaxis is recommended for all patients receiving prednisone doses greater than 20 mg/day. PFTs are recommended with clinical and radiological follow-up at three-month intervals for 1 year after discontinuation of glucocorticoids.

Patients with Severe Respiratory Failure

For patients with rapidly progressive and widespread disease, treatment should be tailored based on the need for mechanical ventilation:

If mechanical ventilation is not required: For these patients, it is recommended to start treatment with intravenous (IV) glucocorticoids. They can be given in divided doses or as a single dose (125-250 mg methylprednisolone every 6 hours or 750-1000 mg/day pulse steroid for 3-5 days).[11] When the patient's oxygen requirement decreases, it is recommended to switch to oral prednisone at a dose of 0.5-1 mg/kg (maximum 60 mg/day).

If mechanical ventilation is required: It is recommended to start treatment with intravenous (IV) glucocorticoids. They can be given in divided doses or as a single dose (250 mg methylprednisolone every 6 hours or 1000 mg/day pulse steroid for 3-5 days).[11] If there is no response within 72 hours, a second agent should be added. Cyclophosphamide is often used (500-750 mg/m^2) because of its rapid effect. However, the choice of treatment in this regard is based on clinical experience.

Treatment for Patients Not Responding to Glucocorticoids

In cases where disease progression is not observed but the response to glucocorticoid therapy is inadequate, alternative diagnoses must be excluded. Once the diagnosis is confirmed, treatment should continue with oral prednisone while initiating a cytotoxic agent. Although there are no definitive recommendations, azathioprine is commonly used. In patients with normal renal function, the dose is started at 50 mg per day. It is recommended to increase the maximum dose (1-2 mg/kg) within 2-4 weeks.

Treatment of Relapses During Glucocorticoid Tapering

Relapses are common during the tapering of glucocorticoid therapy. Therefore, in addition to clinical evaluation, routine follow-up with chest radiographs and pulmonary function tests every 2-3 months is recommended during systemic glucocorticoid treatment. Relapse usually occurs when the glucocorticoid dose is reduced to 15 mg. If there is any evidence of worsening or recurrence of the disease, it is recommended to restart the last and well-tolerated glucocorticoid dose. Relapse is more common in cases of delayed diagnosis and treatment, severe disease with widespread involvement, severe hypoxemia, and lung fibrosis.[16,17]

Long-term treatment with prednisone is recommended for patients with persistent or frequent (more than three) relapses. Azathioprine is recommended for patients who respond to glucocorticoids but require high doses to control disease or who cannot use glucocorticoids because of side effects.

PROGNOSIS

The prognosis for COP is better than for fibrotic lung diseases. Complete recovery occurs in approximately two-thirds of patients treated with glucocorticoids. Symptomatic improvement is sometimes dramatic, occurring within one to two weeks. However, many patients have a slower clinical course, extending from several weeks to several months.

CONCLUSION

Organizing pneumonia (OP) is a rare yet distinct type of interstitial lung disease with a multifaceted clinical presentation and a variety of underlying causes. Its nonspecific symptoms and overlapping radiological findings with other pulmonary conditions pose diagnostic challenges, necessitating a multidisciplinary approach that integrates clinical, radiological, and histopathological evaluations. Glucocorticoids remain the primary treatment modality, offering significant clinical and radiological improvement in most cases, although relapses are common, particularly during dose tapering. Recent advances in understanding the pathophysiology and management of OP underscore the importance of timely and accurate diagnosis to improve patient outcomes while minimizing unnecessary interventions. Future research should prioritize the identification of biomarkers predictive of treatment response and relapse, as well as the development of alternative therapies for cases resistant to glucocorticoids.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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