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# Organizing Pneumonia- Review of Clinical and Radiographic Findings, Treatment and Outcomes

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## ABSTRACT

Organizing Pneumonia (OP) is a clinical condition associated with a histopathologic pattern of lung repair that results from alveolar damage and characterized by a patchy filling of alveoli and bronchioles by loose plugs of connective tissue. Organizing pneumonia is classified as either Cryptogenic OP (COP), which has no specific etiology, or Secondary OP (SOP) which can be associated with a multiplicity of causes such as inflammatory reaction to drugs, infection, collagen vascular disease, malignancy, radiation therapy, etc. The clinical presentation of OP often mimics other disorders such as infection and cancer which can result in the administration of inappropriate antibiotics and a delay in diagnosis and appropriate treatment. The diagnosis of OP often requires histopathologic identification of a predominant pattern of organizing pneumonia and the exclusion of any other possible causes. The treatment usually requires a prolonged steroid course and disease relapse is common.

## INTRODUCTION

Organizing pneumonia (OP) is a clinical condition associated with a histopathologic pattern of lung repair that results from alveolar damage and characterized by a patchy filling of alveoli and bronchioles by loose plugs of connective tissue [1,2]. The term OP has replaced the term bronchiolitis obliterans with organizing pneumonia (BOOP) as the process predominantly affects alveoli and alveolar ducts rather than small airways, although bronchiolitis may coexist [3].

This review will emphasize primary OP, but it must be remembered that the histopathologic pattern of OP can accompany a number of pathologic conditions especially certain cancers and in these cases, it represents an incidental finding and has little clinical significance.

Organizing pneumonia without a known cause is termed primary or cryptogenic (COP) and classified within the scope of idiopathic interstitial pneumonias [4,5]. Secondary organizing pneumonia (SOP) is diagnosed when patients present with the clinical syndrome of OP and have a condition known to be associated with the pathologic pattern of OP [4,6].

SOP can occur in conditions such as inflammatory bowel diseases (IBS), connective tissue diseases (CTD), malignancies, infections, drug reactions, bone marrow or organ transplantations, cancer treatment (including chemotherapy, immunotherapy, targeted therapy), radiation therapy, aspiration, autoimmune disease, occupational exposure, cocaine use and vaping (Table 1).

Table 1: Causes of SOP*.

| Connective tissue dis- ease | Medications** | Infections | Other conditions associated with OP |
|---|---|---|---|
| Polymyositis<br>Dermatomyositis<br>Rheumatoid arthritis<br>Sjogren's syndrome<br>Scleroderma<br><br>Systemic lupus erythematosus | Amiodarone<br>Amphotericin<br>Adalimumab<br>Alemtuzumab<br>Bleomycin<br>Busulphan<br>Carbamazepine<br>Cocaine<br>Check point inhibitors<br>Doxorubicin<br>Durvalumab<br>Eribulin<br>Gold salts<br>Interferon B<br>L-Tryptophan<br>Mesalazine<br>Methotrexate<br>Minocycline<br>Nitrofurantoin<br>Osimertinib<br>Phenytoin<br>Sotalol<br>Sulfasalazine<br>Tacrolimus<br>Ticlopidine<br>Trastuzumab<br><br>**Full list @ pneumotox.com | *Bacteria:*<br>*C.* pneumoniae<br>C. burnetii<br>L.pneumophila<br>M.pneumoniae<br>N.asteroides<br>P.aeruginosa<br>S.marcescens<br>S.aureus<br>S.group B<br>S.pneumoniae<br>M.abscessus<br><br>*Viruses*<br>Herpesvirus<br>HIV<br>Influenza virus<br>Parainfluenza virus<br>Cytomegalovirus<br><br>*Fungi*<br>C. neoformans<br>P. janthinellum<br>P. carinii<br>Aspergillus spp.<br>E. dermatitis<br><br>*Parasites*<br>Plasmodium vivax | *Transplant:*<br>Bone marrow graft<br>Lung transplantation<br>Liver transplantation<br><br>*Hematologic malignancies:*<br>Myelodysplasia<br>Leukemia<br>Myeloproliferative disorders<br>Hodgkin's lymphoma<br><br>*Autoimmune disease*<br>Hashimoto's thyroiditis<br><br>*Miscellaneous:*<br>Lung cancer<br>Sarcoidosis<br>Ulcerative colitis<br>Crohn's disease<br>Sweet syndrome<br>Polymyalgia rheumatica<br>Common variable immunodeficiency<br>Wegener's granulomatosis<br>Polyarteritis nodosa<br>Thyroid disease<br>Cystic fibrosis<br>Coronary artery bypass graft surgery<br>Spice processing<br>Aspiration Radiation therapy<br>Vaping<br>Cocaine use |

*Adapted from Cordier JF. Organising pneumonia. Thorax 2000;55:318–28 [4,6, 21-32]

At least fifty percent of OP cases fall under the heading of COP, but the "cryptogenic" nature

of it may reflect our limited knowledge about other clinical settings that can cause secondary forms. It is important to distinguish between secondary and cryptogenic OP because the management of SOP additionally includes treatment of the underlying disease and avoidance of the offending agent [5,6].

COP is a rare disease. Retrospectively, an incidence of six to seven cases per 100,000 hospital admissions was reported at a major teaching hospital in Canada, in a 20-year review of national statistics for Iceland, the mean annual incidence was found to be 1.1 per 100,000 [7,8].

Men and women are affected equally [9, 10-13]. The mean age of onset is in the fifth to sixth decade of life, only a few cases have been reported in childhood [14]. Tobacco smoking is not considered to be an associated risk factor [1].

Over the past two decades OP has been recognized in association with radiation therapy to the chest wall almost exclusively among breast cancer patients [15]. Estimated incidence of cases is approximately two percent [16]. It usually develops after 2 to12 months of treatment, but occasionally even after two years. Risk factors are unknown, but age above fifty years and concurrent therapy with tamoxifen may be associated with increased risk. Patients present with fever, dyspnea and non-productive cough. The typical radiographic features include peripheral patchy alveolar consolidations, that are always outside the portal of the radiation field and sometimes seen on the contralateral side [18,19]. This is in contrast to radiation pneumonitis which is within the radiation field.

Electronic cigarette use and vaping are emerging causes of lung injury and include a large spectrum of clinical and radiographic presentations. OP has been related to vaping with clinical presentations ranging from subacute to acute hypoxemic respiratory failure. Radiographs also vary from bibasilar consolidations to diffuse ground glass infiltrates. In the few reported cases steroids were the mainstay for treatment with response [19,20].

## CLINICAL PRESENTATION

OP was first described at the beginning of the twentieth century in non-resolving pneumococcal pneumonia cases. Both, cryptogenic and secondary OP have similar presentation with acute or subacute onset with flu-like symptoms (fever, fatigue, myalgia), nonproductive cough, mild dyspnea, and weight loss [1, 33-37]. Symptoms can last for several weeks. In most cases radiographs show consolidations with air bronchograms resembling infectious pneumonia, often in the subpleural distribution (see Figure 1). Antibiotic therapy is commonly given but there is lack of clinical response. Many of the prodromal symptoms typically resolve, but dyspnea may worsen and become the major complaint. Hemoptysis, chest pain and wheezing are unusual. In secondary forms, symptoms may depend on the underlying disease [38-41].

Rarely OP can present as an aggressive, rapidly progressing form with respiratory failure and acute respiratory distress syndrome.

In some instances, patients may be completely asymptomatic with pulmonary findings discovered incidentally on the chest radiograph.

The physical examination is nonspecific. Inspiratory crackles can be present in two-thirds of the patients and are more common in patients with SOP. Clubbing is rare. Twenty-five percent of the patients have a normal physical examination [1,11-13].

**Laboratory Findings and Diagnostic Work-up**

The laboratory findings are nonspecific [7,42,43]. Leukocytosis and neutrophilia are found in 50 percent, increased C-reactive protein in more than 70 percent, increased sedimentation rate in more than 80 percent of cases [3,44].

Pulmonary function tests usually show a mild restrictive pattern [7,13]. Obstructive pattern can be seen in patients with underlying obstructive lung disease. The diffusing capacity for carbon monoxide is usually decreased [5,12,35,44]. Mild hypoxemia with exertion is common.

Flexible bronchoscopy with bronchoalveolar lavage (BAL) is usually done to exclude infection, hemorrhage, and malignancy. BAL is not diagnostic but can show cell counts with a "mixed pattern," including a moderate increase in lymphocytes (25–45 percent), decreased CD4/CD8 ratio (in most cases), neutrophils (approximately 10 percent), and eosinophils (5- 25 percent). Foamy macrophages often are present, and some mast cells and plasma cells may be found [45,46].

Transbronchial biopsy samples are generally not large enough to make a definitive diagnosis of OP, therefore surgical lung biopsy is required in some cases [46].

## RADIOGRAPHIC PRESENTATION

The chest radiograph manifestations of COP in the majority of cases are typically distinctive with bilateral, patchy consolidative or ground glass opacities. Recurrent or migratory pulmonary opacities are common (up to fifty percent of cases) [7]. High resolution computed tomography (HRCT) lung scans are obtained to further evaluate abnormalities (Table 2).

In 90 percent of cases, HRCT demonstrates patchy alveolar opacities, usually lower lobe predominant with subpleural or peribronchovascular distribution. Opacities can be migratory and bilateral. The density of opacities ranges from ground-glass to consolidations with air bronchograms. The size ranges from a few centimeters to an entire lobe (see Figure 1). Often while one area is resolving, another can be forming [9,47-54].

Table 2: Most common radiographic findings in OP.

| Findings | Diffuse airspace opacities (Figure 1 a,b,c) | Solitary pulmonary nodule (Figure 2 a,b) | Infiltrative pulmonary process (Figure 2 c) |
|---|---|---|---|
| Incidence | 90% | 10-15% | <10% |
| Radiographic description | Peripheral, bilateral, often migratory, patchy, subpleural ground-glass opacities or, consolidations with air bronchograms and bronchial dilation. | Usually upper lobes, can cavitate, difficult to distinguish from malignancy and require surgical resection.(figure 2a). Atoll sign (ground-glass opacity surrounded by consolidation, figure 2b). | Diffuse reticular and alveolar opacities. |
| Comment | Confused with pneumonia | Asymptomatic, incidentally found | ARDS, respiratory failure |

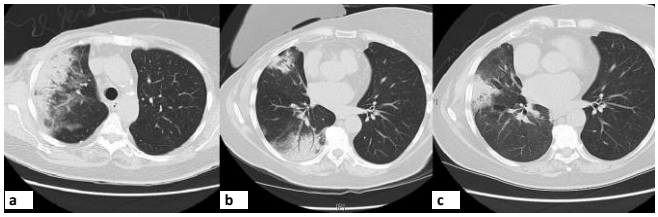


Figure 1: Axial computed tomography scans showing migrating, waxing and waning infiltrates of radiation induced OP in the same patient (a) 3 month after radiation, (b) 9 month after radiation, (c) 18 month after radiation.

In 10 to 15 percent of cases, HRCT shows a solitary pulmonary nodule or mass that is often located in the upper lobe and can occasionally cavitate (see Figure 2a). Some patients are asymptomatic. The diagnosis often requires surgical excision of the lesion as cancer is usually suspected [55-58]. It is not enough to exclude an adjacent peripheral lung cancer based on biopsy showing OP as it might be incidental to the primary pathology. Positron emission tomography (PET) scanning cannot exclude OP in these cases because it is often PET positive mimicking cancer.

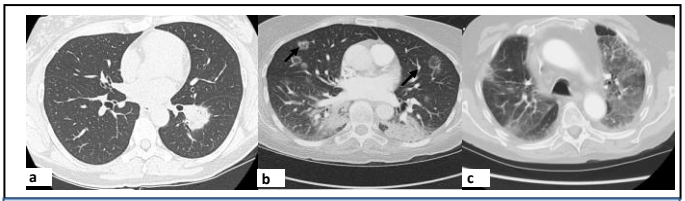


Figure 2(a,b,c): axial computed tomography scans showing COP in patient with sarcoma presenting as a mass mimicking the underlying cancer, 2b- atoll sign -central area of ground-glass opacity surrounded completely or partially by a ring or crescent of consolidation (arrow), 2c - diffuse infiltrative lung disease with reticular and superimposed alveolar opacities .

The “reverse halo” or “atoll” sign is considered to be a characteristic radiographic sign in patients with OP. It represents central area of ground-glass opacity or lucency surrounded completely or partially by a ring or crescent of consolidation (see Figure 2b). Histologically, the central ground-glass area corresponds to alveolar septal inflammation and cellular debris, whereas the outside ring or crescent represents organizing fibrosis within the alveolar and bronchiolar lumina [59-61]. This sign is seen in about twenty percent of patients with OP, but it is nonspecific and can be present in various other infectious and inflammatory conditions.

In less than 10 percent of cases chest imaging demonstrates diffuse infiltrative lung disease with reticular and superimposed alveolar opacities (see Figure 2c). It probably represents an overlap of OP with other interstitial pneumonias including idiopathic pulmonary fibrosis and non-specific interstitial pneumonia [62]. This pattern is commonly associated with progressive dyspnea and respiratory failure.

Another rare form is cicatrial OP with persistent linear opacities as an expression of dendriform pulmonary ossifications which has been described as an unusual cause for a recurrent pneumothorax [63]. COP can also present as diffuse micronodular pattern mimicking miliary lung infiltration [64].

## HISTOPATHOLOGY

The prominent histological finding in OP is numerous buds of granulation tissue representing loose accumulations of collagen-embedded fibroblasts and myofibroblasts within alveoli, alveolar ducts and small airways, usually in a patchy and peribronchial distribution [2].

Intraluminal plugs of granulation tissue may extend from one alveolus to the adjacent one through the pores of Kohn, giving rise to the characteristic "butterfly" pattern (see Figure 3 a,b). Histopathologic appearance is relatively uniform within involved areas. Lesions are usually non- fibrotic and non-destructive. The lung architecture is almost always preserved, although occasionally scarring and remodeling may be seen. [5,12,65]

To make a diagnosis of OP, the pattern of organizing pneumonia must be a prominent feature on the pathology evaluation. It should not be an accessory finding of a different well- defined pattern of idiopathic interstitial pneumonia or an “incidental” finding associated with another disease such as cancer [10,66].

Findings that are not associated with the diagnosis of organizing pneumonia pattern include the presence of prominent cellular and significant interstitial fibrosis, fibroblastic foci, granulomas, hyaline membranes and vasculitis. In OP there is little or no eosinophilia.

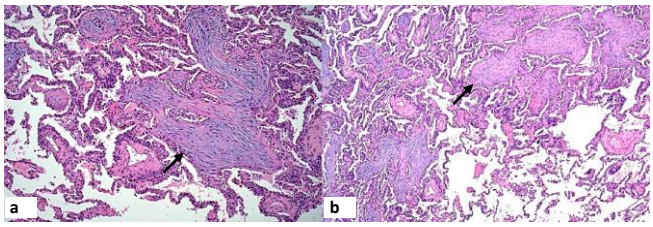


Figure 3 (a,b): showing histopathology of OP: numerous buds of granulation tissue representing loose accumulations of collagen-embedded fibroblasts and myofibroblasts (arrows) within alveoli, alveolar ducts and small airways Figure 3 b showing “butterfly” pattern of OP.

## TREATMENT

Symptomatic patients with OP most often require treatment, spontaneous remissions are rare. Corticosteroid therapy usually results in rapid clinical, radiological and functional improvement in 60-80 percent of cases [2,12,67,68]. Relapses are common, ranging from 13 to 58 percent, and are usually associated with rapid tapering or withdrawal of corticosteroid treatment [67,69]. Relapses occur equally in COP and SOP [4]. If the relapse is diagnosed based on the radiological finding without worsening symptoms, close observation might be enough. Relapses do not appear to have significant effect on morbidity and mortality and do not negatively affect outcome

of the disease [4,11,35,69]. Bronchiectasis, multifocal opacities on chest imaging and a shorter maintenance of the initial steroid dose may increase the risk of relapse [70,71]. COP tends to respond better to treatment than connective tissue disease-related OP (CTD-OP) [72].

Macrolides have an immunomodulatory effect and have been successfully used in treating patients with minimal symptoms and minimal physiologic impairment, or as adjuvant therapy with corticosteroids, and in patients intolerant of corticosteroids [73-77].

Data in support of alternative immunosuppressive agents in cases of corticosteroid-refractory OP are limited. Few case reports have described favorable outcome with azathioprine, cyclophosphamide, cyclosporine and rituximab treatment [78-82].

OP does not require treatment in all cases [68]. Observation or macrolide therapy alone may be adequate in asymptomatic or minimally symptomatic patients.

Focal forms of OP have a very good prognosis as the lesion is usually surgically removed because it mimics cancer, although some patients may experience recurrent disease [83,84].

The mortality of OP has been reported to vary from five to 27 percent with rates higher with SOP than COP, but it is difficult to ascertain whether this is due to progression of OP or other complicating conditions [9,34].

## OTHER FORMS OF ORGANIZING PNEUMONIA

Rare forms of OP have been described and include acute fibrinous and organizing pneumonia (AFOP) and granulomatous organizing pneumonia (GOP).

AFOP can have an acute or subacute clinical presentation of cough and/or dyspnea. Some cases can lead to rapid respiratory failure requiring mechanical ventilatory support. Chest imaging usually shows diffuse patchy ground glass opacities (see Figure 4a). The pattern of lung injury is different from the classic patterns of diffuse alveolar damage (DAD) or eosinophilic pneumonia. Predominant histologic features of AFOP include organizing intra-alveolar fibrin balls in a patchy distribution in addition there may be an OP pattern consisting of intraluminal loose connective tissue within alveolar ducts and bronchioles associated with the fibrin (see Figure 4b,c). The mainstay of treatment is steroids. Subacute presentations have a better prognosis compared with those patients presenting with rapidly developing respiratory failure [86].

Granulomatous organizing pneumonia (GOP) is a recently described variant of OP [87]. Patients usually are asymptomatic but can present with cough, fever and chills. In the small number of cases reported the predominant radiographic pattern was nodules (see Figure 5a). The histopathologic pattern shows an organizing pneumonia in close association with small poorly formed non-necrotizing granuloma confined to the same peribronchial location and within the OP pattern (see Figure 5b,c).

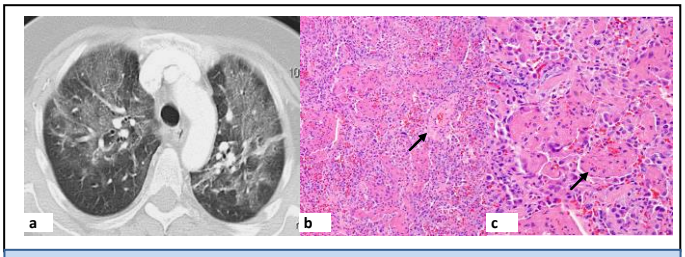


Figure 4: (a) axial computed tomography with diffuse ground glass opacities, (b,c) classic finding of AFOP: intra-alveolar fibrin in the form of "fibrin balls" without formation of hyaline membranes (arrows).

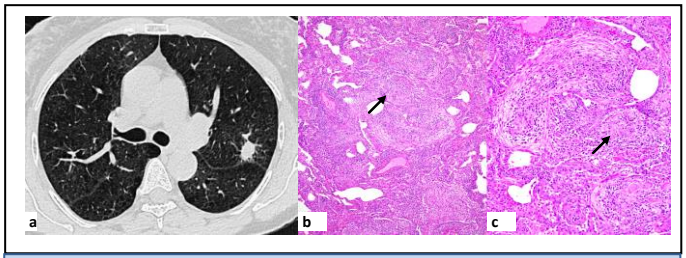


Figure 5: (a) axial computed tomography of chest showing nodule of GOP, (b and c) small poorly formed non-necrotizing granulomas of GOP (arrows).

## CONCLUSION

The clinical presentation of the various OP's (COP, SOP, AFOP, GOP) often mimics other disorders such as infection and cancer which may result in the administration of inappropriate antibiotics and a delay in diagnosis and appropriate treatment. The diagnosis of OP often requires histopathologic identification of the predominant pattern of the organizing pneumonia and the exclusion of any other possible causes especially infection and cancer. Hence the input of an experienced pathologist is essential to making the proper diagnosis. It is also important to distinguish idiopathic (i.e. COP)

from secondary forms of OP (SOP). The treatment usually requires a prolonged steroid course and disease relapse is common.

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