Cryptogenic organized pneumonia: Case report and literature review

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World Journal of Advanced Research and Reviews, 2022, 15(02), 488–496

Publication history: Received on 11 July 2022; revised on 18 August 2022; accepted on 20 August 2022

Article DOI: https://doi.org/10.30574/wjarr.2022.15.2.0841

Abstract

Introduction: cryptogenic organized pneumonia is a clinical, radiological and histological entity classified as interstitial lung disease.

Case Report: A 40 year old man had initially consulted for influenza-like syndrome. Our clinical examination founded dry crackling rails in bilateral lungs, the tomography showed condensation fireplace and bilateral ground glass fireplaces in relation to the condensing foci seat by place of sub-pleural cross-linkings achieving an aspect of crazy paving, ground glass fireplace surrounded by condensation achieving the aspect of inverted halo. The patient was initially treated as bacterial pneumonia but without improvement under multiple antibiotic therapies. Bronchoscopy had objectified an endoscopic appearance without particularity. The etiological assessment was negative. The diagnosis of cryptogenic organized pneumonitis in its was retained. Systemic corticosteroid therapy was prescribed and the assessment at 3 months, 5 months of treatment had noted a clear and frank improvement clinically and radiologically with a relapse at the 9 Th month following the stop a corticosteroid therapy.

Discussion: Cryptogenic Organizing Pneumonia, was recently defined by an ATS/ERS consensus conference. Diagnosis is established by combining clinical, radiological and histological criteria. Most patients respond well to corticosteroid therapy. Relapses are frequent but can generally be controlled with moderate doses of prednisone.

Conclusion: POC has become a well-characterized entity among idiopathic interstitial lung diseases. It is characterized by a usual clinic-radiological presentation, often with a good prognosis and their management requires a multidisciplinary approach.

Keywords: Bronchiolitis obliterans; Organizing pneumonia; Secondary organized lung disease; Idiopathic interstitial lung disease; Cryptogenic organized Pneumonia; Interstitial lung disease

1. Introduction

Organizing pneumonia (OP), formerly known as bronchiolitis obliterans, is a clinical, radiological and histological entity classified as interstitial lung disease [1]. It can be idiopathic and of unknown etiology that is called cryptogenic organized pneumonia (COP) and can also be secondary to many etiologies, such as inflammatory infections, drug responses, pulmonary infarction, pleural injury, tumor chemotherapy agents, and connective tissue disease [2]. The pathology of COP includes inflammatory cell infiltration, interstitial fibrous tissue hyperplasia with increased fibroblast proliferation and granulation tissue formation in the alveolar space. In most cases, the radiological presentation is characterized by multiple airspace consolidations with subpleural distribution or areas of ground glass lung infiltration, however, many other unusual presentations have also been reported [3-5].
In this report, we report the case of a 38-year-old patient with COP simulating a picture of sars cov 2 infection and describe the clinical, radiological, and diagnostic features of cryogenic organizing pneumonia (COP) according to the literature.

2. Case Report

Our patient was 40 years old, male, driver in a phosphate production unit, never treated for pulmonary tuberculosis and without recent contagion, having as ATCD an exposure to industrial gases, occasional user of tobacco and kiff and weaned alcoholic.

The patient had initially consulted for a flu-like syndrome, dry cough, dyspnea stage II of Sadoul, chest pain of moderate intensity, associated with extra thoracic signs such as polyarthralgia, evolving in a context of feverish sensations and decline of the general state (weight loss of 11 kg), it should be noted that the patient was initially treated as bacterial pneumonia but without improvement under multiple antibiotic therapies.

On clinical examination: patient conscious SG 15/15, polypneic at 26 cpm, SaO2 at 96% at room air, no sign of respiratory struggle, PS WHO at 1, no digital hippocrasis, on pleural-pulmonary auscultation dry crackling rales in bilateral basithoracic focus.

The frontal radiography showed multiple alveolar opacities in bilateral migratory patches, predominantly in the subpleural and peripheral regions, confluent in places, of migratory character and variable size (Figure 1, 2, 3).

![Figure 1](image1.png) Multiple alveolar opacities in migratory bilateral beaches predominant in the subepural and peripheral region sat their confluences in places (13/4/2021)

![Figure 2](image2.png) Migratory character of variable size(23/4/2021)

![Figure 3](image3.png) Migratory character of variable size(26/4/2021)
A thoracic CT scan was requested as part of the etiological work-up in the face of non-improvement with antibiotic therapy, which revealed lower lobar alveolar condensations (Figure 4,5), annular ground glass opacities surrounded by a peripheral consolidation halo: Inverted Halo Sign (Figure 6).

The patient was initially thought to have organized pneumonia associated with SARS-CoV-2 pneumonia in view of the pandemic, and non-improvement on antibiotic therapy, an RT-PCR test of the nasopharyngeal swab was negative.

![Figure 4 and 5 Inferior lobar alveolar condensations](image1)

![Figure 6 Annular ground glass opacities surrounded by a peripheral halo of consolidation: Halo sign](image2)

High resolution chest CT scan with millimeter slices at 16 day intervals revealed foci of migrating condensation specifically: Foyer of condensation in the form of a patch visible in the apical and dorsal segments of the LSD, right Fowler, right later and poster basal, seat of air bronchogram, bilateral ground glass foci opposite the foci of condensation, seat in places of sub pleural reticulations producing a crazy paving aspect, ground glass foci surrounded by condensation producing the aspect of an inverted halo, more marked at the bilateral apical level (Figure 7).

Laboratory examinations showed that the patient had a white blood cell count of 16400/ L with predominance of neutrophils at 13260, a normal lymphocyte level at 1940, anemia at 10.6 g/dl; the myelogram was in favor of normocytic normochromic anemia with slight excess plasma cell in connection with an inflammatory or infectious process and a platelet count of 508000. CRP was elevated to 168 mg/l and sedimentation rate was 85 in the 1st hour and 110 in the 2nd hour. Electrolytes, creatinine levels, liver function were normal.
Bronchoscopy showed an unremarkable endoscopic appearance apart from the presence of an anthracitic stain in the left posterior basal area. The bronchial biopsy was staged on the right and left sides and was not contributive. The BAL showed a variegated alveolitis with high total cellularity, predominantly lymphocytic. The cytobacteriological examination of the bronchial suction fluid showed a mixed flora culture below the threshold, the search for BK and GeneXpert, as well as the mycological study in the bronchial suction fluid were negative.

**Figure 7** Ground glass foci surrounded by condensation producing the aspect of an inverted halo (19/04/2021)

Sars-cov-2 PCR and covid IgM and IgG serologies were negative, respiratory PCR was positive for Human Rhinovirus

Serum protein electrophoresis was consistent with a significant inflammatory syndrome. The immunological blood test (AAN, FR, anti-SSA, anti-SSB, and anti-CCP) was negative as well as the determination of the conversion enzyme.

Aspergillus serology and prick test were also negative. The arterial gasometry was normal.

In view of the evocative radio-clinical picture, and the negative etiological work-up, the diagnosis of cryptogenic organized pneumopathy in its subacute form was retained. Systemic corticosteroid therapy was prescribed orally: Prednisone at a dose of 0.75 mg/kg/day for 4 weeks, then tapering off over 6 to 12 months.

**Evolution:** Evaluation at 3 months, 5 months of treatment had noted a clear clinical and radiological improvement (Figure 8)

**Figure 8** Spectacular radiological clean-up under systemic corticosteroid therapy argues for POC
Figure 9 Scannographic clean-up with banded middle lobe atelectasis, apical paraseptal emphysema bullae (12/9/2021)

Our patient presented a relapse in the 9th month following the stop a corticosteroid therapy (Figure 10)

Figure 10 Ground glass foci in the middle lobe (December 2021)

3. Discussion

Organized pneumonitis (OP) is a particular form of inflammatory reaction of the lung parenchyma characterized by proliferation of myofibroblasts in the distal airspaces, without destruction of the surrounding lung parenchyma architecture. It was not until the 1980s that the clinical syndrome of organized lung disease was described, combining general and respiratory symptoms, and multiple radiological opacities, responding rapidly to treatment with corticosteroids [6].

3.1. Terminology

The term bronchiolitis obliterans with organized lung disease (BOOP) is abandoned in favor of organized lung disease. The term organized lung disease is reserved for the clinic-radiological syndrome. Organized lung disease may be cryptogenic or secondary. The term "organized lung disease appearance" refers to the histological entity in which granulation tissue buds filling the alveolar spaces are the primary lesion. [7]

3.2. Epidemiology

The only study on the epidemiology of OP has been done in Iceland. In this retrospective study, which only took into account biopsy-proven cases (and therefore certainly underestimated the true incidence), the authors reported an annual incidence of OP of 1.97 cases per 100,000 population. Of the 104 cases, 44% were secondary OP and 56% POC. There was no difference in incidence between men and women. Almost all cases occurred after the age of 45 years, on
average at the age of 67 years. Extrapolation of these data to France suggests the occurrence of over 1000 new cases per year [8].

3.3. Pathogenesis
Organized lung disease is characterized by the formation of collagen-rich intra-alveolar connective buds, without significant involvement of the pulmonary interstitial. The sequence leading to the formation of these intra-alveolar buds is now well defined. Animal models, as well as some observations in humans, suggest that T cells play a central role in the pathogenesis of organized lung disease [9].

3.4. Clinical picture
The clinical presentation of cryptogenic organized lung disease is not specific, with cough, dyspnea and a febrile state mimicking infectious lung disease being the most common symptoms. Auscultation may reveal fine crackling rales. Rarely, cryptogenic lung disease may be asymptomatic or conversely result in acute respiratory failure 10, 11,12,13,14,15,16].

Table 1 Average, minimum and maximum frequencies of symptoms and signs present at the diagnosis of organized pneumonitis, established from 7 series of more than 20 cases (n = 433) [10, 11,12,13,14,15,16].

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Average (%)</th>
<th>Min (%)</th>
<th>Max (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>8</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td><strong>General symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>61</td>
<td>50</td>
<td>76</td>
</tr>
<tr>
<td>Weight loss</td>
<td>34</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>32</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Malaise/asthenia</td>
<td>43</td>
<td>21</td>
<td>72</td>
</tr>
<tr>
<td>Night sweats</td>
<td>21</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td><strong>Respiratory symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>73</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>59</td>
<td>40</td>
<td>86</td>
</tr>
<tr>
<td>Chest pain</td>
<td>28</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>8</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td><strong>Clinical signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine crackling</td>
<td>73</td>
<td>49</td>
<td>84</td>
</tr>
<tr>
<td>Sibilances</td>
<td>17</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>Hippocratism digital</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

3.5. Biology
The blood workup shows an inflammatory syndrome with elevated C-reactive protein and hyperleukocytosis. This clinical picture is therefore often mistaken for infectious pneumonitis, and the diagnosis is often suspected only after an unsuccessful attempt at antibiotic treatment [17].

3.6. Imaging
The two main radiological presentations of cryptogenic organized lung disease are plural focal alveolar condensations and single nodule. Migrating opacities are fairly suggestive of the diagnosis of organized lung disease, whereas the more recently described inverted halo sign is not specific. Focal organized lung disease can have a radiological presentation quite similar to that of pulmonary neoplasia, including its appearance on PET scan.
Table 2 Clinical and radiological characteristics of patients with focal cryptogenic organized lung disease, in 6 case series

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>26</td>
<td>14</td>
<td>26</td>
<td>21</td>
<td>45</td>
</tr>
</tbody>
</table>

**Clinical features**

<table>
<thead>
<tr>
<th></th>
<th>Men %</th>
<th>Smokers or ex-smokers, %</th>
<th>Symptoms, %</th>
<th>Cancer concomitant, %</th>
<th>Recent infection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56</td>
<td>69</td>
<td>17</td>
<td>15</td>
<td>39</td>
</tr>
</tbody>
</table>

**Radiological aspect**

<table>
<thead>
<tr>
<th>Average size, mm</th>
<th>20</th>
<th>-</th>
<th>20</th>
<th>19</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme size values</td>
<td>9—66</td>
<td>-</td>
<td>6—68</td>
<td>10—50</td>
<td>10—55</td>
</tr>
<tr>
<td>Nodules satellites, %</td>
<td>56</td>
<td>38</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Bronchogramme aérique, %</td>
<td>50</td>
<td>-</td>
<td>8</td>
<td>5</td>
<td>56</td>
</tr>
<tr>
<td>Mediastinal lymphadenopathies %</td>
<td>-</td>
<td>19</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

3.6.1. Bronchoalveolar lavage

BAL is usually performed in cases of suspected OP because it can rule out an infectious cause and because the cellular distribution may reinforce the clinical probability of OP or identify other types of infiltrative lung disease, particularly eosinophilic lung disease, which may resemble POC in radiological presentation. In OP, BAL shows increased cellularity and mixed (variegated) alveolitis, with lymphocytic predominance (20-40%), and mild elevation of neutrophils (10-15%) and eosinophils (about 5%) [24,25,26]

3.6.2. Histology

The definite diagnosis of organized lung disease usually requires a compatible clinical presentation and histological evidence. Surgical biopsies provide a more reliable diagnosis, but transbronchial biopsies are an acceptable alternative if the radio-clinical picture is typical. Intra-alveolar connective buds, the characteristic elementary lesions of organized lung disease, are not specific and may occur incidentally in other lung diseases. Only when these lesions predominate and there is no evidence for an alternative diagnosis can a histological picture of organized lung disease be accepted. A bronchoalveolar lavage is performed in almost all cases, and classically shows a "patchy" cell distribution. When the diagnosis of organized lung disease is made, all potential causes of secondary organized lung disease must still be investigated before a cryptogenic form can be concluded [14,15,16].

3.7. Treatment

Monitoring without treatment is possible in forms of nodular cryptogenic organized lung disease after surgery, and in a few cases of asymptomatic multifocal cryptogenic organized lung disease with no functional impact. Corticosteroids remain the treatment of choice in the vast majority of cases of cryptogenic organized lung disease. Although the optimal regimen has not been established, it is suggested that the GERM\(^\circ\) P regimen, which has been shown to be effective while reducing the cumulative dose of corticosteroids. There is still insufficient data on the use of macrolides for anti-inflammatory purposes in cryptogenic organized lung disease to recommend this treatment [27].
### Table 3 Treatment regimen for cryptogenic organized lung disease [27]

<table>
<thead>
<tr>
<th>Step</th>
<th>Duration (weeks)</th>
<th>Dose of prednisone For episode initial</th>
<th>Dose of prednisone relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0,75 mg/kg/j</td>
<td>20 mg/jr</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0,5 mg/kg/j</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>20 mg/j</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>10 mg/j</td>
<td></td>
</tr>
</tbody>
</table>

### 3.8. Relapse and prognosis

In the vast majority of cases, cryptogenic lung disease responds completely or partially to corticosteroid treatment. Its prognosis is significantly better than that of most other interstitial lung diseases, although there appears to be a small subgroup of patients who may have a severe form of cryptogenic organized lung disease. Relapses during or after cessation of treatment are common; they respond well to increased steroid doses and do not impact on prognosis [14, 15, and 27].

### 4. Conclusion

Since its first clinical descriptions in the 1980s, POC has become a well-characterized entity among idiopathic interstitial lung disease. Alongside the usual clinico-radiological presentations, which often have a good prognosis, there are cases of POC that are more resistant to treatment, possibly representing overlapping forms with non-specific interstitial lung disease. Animal models and some observations in humans suggest that T cells play a central role in the pathogenesis of OP. Mechanisms for fibroblast bud resolution include extracellular matrix composition (particularly the type of collagen deposited), matrix metalloproteinase activity, and angiogenesis and apoptotic activity. A better understanding of these mechanisms may open up new avenues of treatment for other types of diffuse infiltrative lung disease. While corticosteroid therapy is usually very successful in POC, its unfavorable side-effect profile should prompt investigation of the role of alternative treatments such as macrolides.

### Compliance with ethical standards

#### Acknowledgments

Thanks to the reviewers for their insightful comments and help in constructing this article.

#### Disclosure of conflict of interest

Authors declare that they have no links of interest.

#### Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

### References


