Bronchiolitis obliterans organizing pneumonia

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ABSTRACT

Bronchiolitis obliterans with organizing pneumonia (BOOP) is now established as a distinct clinicopathologic entity, yet it may be overlooked by clinicians due to unfamiliarity and its non-specific presentation. It can be either idiopathic or associated with a variety of causes, such as infections, drugs, radiation or connective tissue diseases. A lung biopsy is needed to provide histopathologic confirmation. Usually prognosis is good, and the response to steroids may be dramatic, but occasionally BOOP may be fatal or runs a chronic relapsing course. This article is an updated review on current knowledge regarding BOOP.

conditions were associated with BOOP, the nature and extent of the association still awaits further studies. Recently, BOOP has been identified to occur after adjuvant radiotherapy for breast cancer with a time frame of 2-6 months. This needs to be distinguished from radiation pneumonitis, which usually occurs within radiation field. However, it has been argued that due to the migratory nature of BOOP, it may initially originate at site of radiation field and then migrate with time.90 Finally, smoking has not been directly linked as an etiologic factor of BOOP.5,100

Clinical manifestation. The disease onset is typically in the fifth or sixth decades of life, but it can occur over a wide age range (12-85 years), with men and women affected equally. Most of the patients (>70%) are asymptomatic, usually for a period that is less than 2 months before presentation, and only few have symptoms for more than 6 months before diagnosis. The most common presenting symptoms are dyspnea, fever, and non-productive cough (Table 2). Fever is continuous and low grade or intermittent in 41%, while 23% present with acute fever, leading to the incorrect diagnosis of bacterial pneumonia. In 30-50%, the onset is preceded by flu-like illness for 3-4 weeks. Physical examination revealed inspiratory crackles in 79% and rarely wheezes.5,8,100,101 Clubbing is a rare feature of BOOP.

Laboratory findings. Routine laboratory studies are non-specific.6,15,100,102 Leukocytosis is present in 50% of patients, with a slight eosinophilia in 8%.100 Erythrocyte sedimentation rate (ESR) exceeds 30 mm in 80%,100 Lactate dehydrogenase (LDH) is elevated in 20–25%.100 Autoantibodies are usually negative or present in very low titer.100,103

Roentgenographic manifestation. The radiographic abnormalities are summarized in (Table 2). Bronchiolitis obliterans organizing pneumonia has a characteristic radiographic pattern that may suggest the diagnosis. Bilateral opacities occur in most of patients (Figure 1), but a few patients may have unilateral disease.61,104 The distribution may be found in the lower zone in 60–70% of patients, in the middle zone in 25-30%, and in the upper zone in 20–30%.6,100 The typical picture is usually of bilateral patchy alveolar opacities in 40-70%, reticulonodular opacities in 6%, and both patchy infiltrate and reticulonodular opacities in 12% of patients.6,104 Serial radiographic may demonstrate migration of opacities in 50-50% of patients. Other uncommon findings are presence of pleural effusion, pleural thickening, hyperinflation, atelectasis, solitary pulmonary nodule, and pneumothorax.1,100,105-107 Bronchiolitis obliterans organizing pneumonia can present rarely as cavitory lesion resembling pulmonary tuberculosis.108 High resolution computed tomography (HRCT) scan usually shows characteristics abnormalities. Pleural-based alveolar opacification is the most frequent imaging abnormalities (Figure 2).5,6,9,100,109 However, areas of ground glass attenuation are detected in 15%, in which radiographically the lesion appeared to be focal. Furthermore, linear opacities may be the sole abnormalities on HRCT, which may be either external in a radial manner along the line of the bronchi towards the related pleura, or in a sub-pleural location that have no relation to the bronchi.110 Honeycombing is usually absent.

Physiological finding. Pulmonary function tests are usually abnormal; restrictive impairment with a reduced forced vital capacity (FVC) as well as an impaired gas exchange are the most commonly detected abnormalities.9 Forced vital capacity is reduced (<80%) in 60% of patients.10 Much common, patients with BOOP may have an obstructive defect with a decreased forced expiratory volume in the first second (FEV1)/FVC ratio (<70%) in 10–20%, although this is usually present in smokers. Diffusion capacity for carbon monoxide (DLCO) is typically reduced (<80%) in most patients. Widening of resting alveolar arterial oxygen gradient and exercise-related hypoxemia are common abnormalities (80%).9,109 This could be explained by intrapulmonary shunt at the capillary level as of intra-alveolar organization in the absence of anatomical right-to-left shunt.111

Bronchoalveolar lavage. Bronchoalveolar lavage (BAL) is an important diagnostic tool in BOOP, particularly to diagnose any associated or underlying disease. In addition, it may be useful in excluding other diseases that mimic BOOP, particularly chronic eosinophilic pneumonitis and interstitial pulmonary fibrosis.

The profile of the differentiated white cell count in BAL fluid was assessed by several groups with similar results. Bronchoalveolar lavage fluid usually shows a mixed pattern, but typically the percentage of lymphocytes predominates in up to 65% of patients, with increase in neutrophils (10%) and eosinophils (5%) in many cases. Other features include the frequent presence of foamy macrophage, mast cell, and plasma cells. CD4+/CD8+ ratio is significantly decreased and this is seen in 50-60% of patients. However, a few percentages may have increased CD4+/CD8+ ratio. In a few cases, atypical epithelial cells (cytokeratine + positive cells) are detected. Several cytokines are typically increased in BOOP; this includes IL 10, IL 12, and IL 18.114

Histopathology. Tissue diagnosis of BOOP is usually required, and a transbronchial biopsy (TBB) is a minimally invasive method that can be initially employed in most patients. However, since the involvement of lung in most of the cases is patchy, TBB may not be diagnostic. In such situation, a lung biopsy may be indicated through a video-assisted
Table 1 - Causes and associated conditions with bronchiolitis obliterans organizing pneumonia.

<table>
<thead>
<tr>
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<th>Connective Tissue Diseases</th>
<th>Drugs</th>
<th>Miscellaneous</th>
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<td><strong>Viruses</strong></td>
<td>Bechet’s disease</td>
<td>Acetabutol66</td>
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<td>Herpes virus16,17</td>
<td>Mixed connective tissue</td>
<td>5-Aminosalicylic acid57</td>
<td>Common variable immunodeficiency</td>
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<tr>
<td>Human immunodeficiency virus18-20</td>
<td>5-Aminosalicylic acid57</td>
<td>Amiodarone67</td>
<td>syndrome 7</td>
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<td>Influenza virus21-22</td>
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<td>Amphotericine B60</td>
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<td>Carbamazepin63</td>
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<td>Chlamydia pneumoniae24,25</td>
<td></td>
<td>Cephalosporin9,60</td>
<td>Leukemia10,80</td>
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<tr>
<td>Coxiella burnetii26,27</td>
<td></td>
<td>Cocaline69</td>
<td>Liver transplant61</td>
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<td>Legionella pneumophila21,28,29,33</td>
<td></td>
<td>Gold13</td>
<td>Lung transplant63</td>
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<td>Mycoplasma pneumoniae21,28,34</td>
<td></td>
<td>Interferon56,66</td>
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<td>Pseudomonas aeruginosa16</td>
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<td>Methotrexate60</td>
<td>Renal transplant89</td>
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<td>Staphylococcus aureus10</td>
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<td>Minocycline68</td>
<td>Sarcoidosis57</td>
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<td>Streptococcus group B38</td>
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<td>Naphroxen8</td>
<td>Seasonal syndrome with cholestasis96</td>
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<td>Streptococcus pneumoniae39,41</td>
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<td>Nitrofurantoin69</td>
<td>Spite processing67</td>
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<td><strong>Parasites</strong></td>
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<td>Phenytoint1</td>
<td>Sweet’s syndrome96</td>
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<td>Malaria32</td>
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<td>Sotalol72</td>
<td>Thyroid disease99</td>
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<td><strong>Fungi</strong></td>
<td></td>
<td>Sulindac60</td>
<td>Ulcerative colitis57,80</td>
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<td>Cryptococcus neoformans41</td>
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<td>Sulphamethoxyridazine60</td>
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<td>Penicillium janthinellum44</td>
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<td>Sulphasalazine60</td>
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<tr>
<td>Pneumocystis carinii (in AIDS)16,45,46</td>
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<td>Tacrolimus73</td>
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<td><strong>Miscellaneous</strong></td>
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<td>Ticlopidine74</td>
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Table 2 - Clinical and roentgenographic manifestation in different studies.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Epler et al1</th>
<th>Cordier et al5</th>
<th>Bellomo et al109</th>
<th>Costabel et al6</th>
<th>Izumi et al6</th>
<th>Kings et al8‡</th>
<th>Cazzato et al100</th>
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<td><strong>Clinical manifestation</strong></td>
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<td></td>
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<tr>
<td>Fever</td>
<td>28</td>
<td>88</td>
<td>50</td>
<td>71</td>
<td>53</td>
<td>46</td>
<td>63</td>
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<td>88</td>
<td>83</td>
<td>71</td>
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<td>83</td>
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<td>47</td>
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<td>63</td>
<td>100</td>
<td>79</td>
<td>76</td>
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<td>35</td>
<td>71</td>
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<td>48</td>
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<td>Crackles</td>
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<td>100</td>
<td>86</td>
<td>79</td>
<td>75</td>
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<td>Clubbing</td>
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<td>6</td>
<td>0</td>
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<td>3</td>
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<td>Smoker</td>
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<td>21</td>
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<td>17.8</td>
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<td>NA</td>
<td>56</td>
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<td><strong>Chest radiograph</strong></td>
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<td>Diffuse</td>
<td>69</td>
<td>25</td>
<td>33</td>
<td>100‡</td>
<td>68</td>
<td>68</td>
<td>80§</td>
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<tr>
<td>Localized</td>
<td>4.8</td>
<td>31</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
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<td>Reticulomodular</td>
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<td>0</td>
<td>0</td>
<td>6</td>
<td>Rare</td>
<td>17</td>
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</table>

* values are presented as a percentage, NA - not available
† 13 patients had bilateral diffuse patchy infiltrates and one patient has unilateral infiltrate
‡ smoking history available in 79 patients, chest radiograph available in 100 patients
§ 31 patients have bilateral diffuse patchy infiltrates and 31 patients have unilateral infiltrates

*Thoracoscopic (VATS) approach or via a formal thoracotomy. This provides a large lung specimen, which allows the diagnosis to be made with confidence and help in excluding other associated diseases. Lung biopsy specimens are considered positive for BOOP if they showed buds of granulation tissue (Masson bodies) within the small airways and alveoli (Figure 3). Other features include the infiltration of alveolar wall with chronic inflammatory cells, which are composed of histiocytes, lymphocyte, and plasma cells, but the alveolar architecture is otherwise maintained.

**Differential diagnosis.** The symptoms and chest radiographic findings as seen in BOOP are also seen in infectious pneumonia. However, infectious pneumonia (except viral pneumonia) usually responds to antibiotics. Wegener's granulomatosis may be also confused with BOOP, but presence of extra-thoracic involvement in Wegener's granulomatosis help in differentiation.
Occasionally, it is difficult to distinguish BOOP from acute interstitial pneumonitis (AIP). However, presence of honeycombing, traction bronchiectasis interlobular septal thickening, and interlobular reticular opacities on HRCT, and the absence of lymphocytosis in BAL support AIP more strongly than BOOP. Chronic eosinophilic pneumonitis (CEP) can also be difficult to distinguish from BOOP. However, the following features may help: 1. Clubbing is seen more frequently in CEP than BOOP. 2. The migration of the infiltrates is seen more frequently with BOOP (50% versus 7%); 3. A computerized tomograph scan finding showing the presence of nodules or a mass followed by non-septal linear or reticular opacities is more frequently seen in BOOP than CEP. Also, bronchial dilatation is more characteristic of BOOP, and bronchoalveolar lavage cell findings revealed that the percentage of lymphocytes exceed that of eosinophilic in patients with BOOP than patients with CEP (96% versus 55%).

**Treatment.** Up to date, corticosteroids remain the standard treatment, and are quite effective in most cases of idiopathic BOOP. Complete clinical recovery, physiological improvement, and normalization of the chest radiograph are seen in 70% of patients. Approximately 25-30% of patients demonstrate persistent disease and 5% may progress rapidly to respiratory failure and death. Clinical improvement is usually rapid and may be dramatic occurring within few days but it might take few weeks. Occasionally, recovery is quite dramatic. Relapses may occur on reducing the dose of corticosteroids or shortly after stopping therapy.
in 25% of case. Most patients who relapse show improvement when therapy is restarted. Spontaneous improvement may occur in a few patients over 3-6 months. Most patients with patchy alveolar pattern showed rapid and good response to therapy.

The optimal dosing and duration of steroid therapy have not been determined yet by controlled studies. Many experts recommended starting therapy with prednisone in a dose of 1-1.5 mg/kg per day. The dose is maintained for 4-8 weeks. If the patient’s condition is stable or improved, the dose is gradually reduced to 0.5 mg/kg per day for the ensuing 4-8 weeks, and then tapered off after 3 to 6-months. High dose steroid (IV methylprednisolone) 1 gm per day for 3-5 days may also be given to patients especially with rapidly progressive BOOP. Serial chest radiograph and PFT are helpful in monitoring the patient’s condition every 4-6 weeks especially during the first year. If there are any signs of recurrence, therapy has to be restarted aggressively.

In case patient's condition does not improve despite aggressive treatment with an adequate dose of corticosteroid, cytotoxic agents may be added. However, due to the limited data on their efficacy, these drugs should be reserved as salvage therapy for patients with progressive and life threatening disease, which are unresponsive to corticosteroid.

Cyclophosphamide was reported to be effective in a few case reports. It is used in a single daily dose of 1-2 mg/kg per day; the dose is slowly increased over 2-4 weeks. Maximal dose should not exceed 150 mg per day. Alternately pulse therapy with a dose similar to that used in the treatment of Wegener's granulomatosis maybe used in rapidly progressive disease. Drug complications, which include bone marrow suppression and hemorrhagic cystitis, need to be recognized and the dose should be adjusted. Azathioprine has also been employed in treatment of BOOP, and can be used as corticosteroid sparing agent in difficult cases of BOOP that require prolonged treatment with high dose corticosteroids. This drug is tolerated by most patients, but serious side effect such as bone marrow suppression, hepatitis, and pancreatitis may occasionally occur. Other drugs that were reported to be effective in BOOP include cyclosporin A, pirenidone, methotrexate, and erythromycin. Experience with these drugs remains preliminary, and more rigorous trials are needed to determine their efficacy.

**Prognosis.** Bronchiolitis obliterans organizing pneumonia is a benign disease that responds well to corticosteroids. However, due to the lack of long-term prospective studies, little is known regarding the eventual outcome. A number of retrospective studies suggest that most patients have a good prognosis, and that some patients might even remit spontaneously. However, there are subgroups in whom progressive disease develops leading to Acute Respiratory Distress Syndrome (ARDS), and die from respiratory failure.

Factors that may be associated with a poorer prognosis include: 1. Radiographic imaging showing interstitial or mixed alveolar and interstitial infiltrates as opposed to alveolar infiltrates. 2. Bronchoalveolar lavage showing an excess of neutrophils or eosinophils, or both more than lymphocytes. 3. Presence of an underlying condition such as connective tissue diseases, (except for some studies that showed good prognosis in association with rheumatoid arthritis) This may be related to the presence of other pulmonary manifestations of these diseases, for example interstitial pulmonary fibrosis that has a worse prognosis. 4. Delayed treatment may be associated with frequent relapses. 5. Hepatic cholestasis was found to be a risk factor in one study. Relapses do not affect outcome, and prolonged therapy to suppress relapses appears unnecessary.

In conclusion, BOOP is an uncommon but now a well recognized clinicopathologic entity. Although most cases are idiopathic, an underlying systemic disease, infection, or exposure to drugs or radiation may be implicated. The clinical presentation is not specific, which may cause confusion with other acute pulmonary disorders, particularly pneumonia. Although certain clinical and radiological features may give clues to the diagnosis, histopathologic confirmation is often required. Bronchiolitis obliterans organizing pneumonia usually responds well to corticosteroid therapy and typically runs a benign course. However, relapses can occur when steroids are tapered or stopped. Controlled trials are still needed to determine the optimal use of corticosteroids and the potential benefits of other therapeutic agents.

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Cryptogenic organizing pneumonitis.


Bronchiolitis obliterans organizing pneumonia.


Bronchiolitis obliterans organizing pneumonia.


Cryptogenic organizing pneumonitis.


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