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.

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Bronchiolitis obliterans organizing pneumonia (BOOP) is a clinicopathological syndrome, which has gained an increasing attention the last decade. In Europe it is known as cryptogenic organizing pneumonia (COP). Most cases of BOOP are idiopathic. However, several retrospective studies and a large number of case reports have linked BOOP to certain associated systemic diseases or causative agents.[1-11]

The incidence and prevalence is still unknown. A prevalence of 6-7 per 100,000 admissions was reported,[12] but it is likely that this figure may increase over the next years in the presence of increasing conditions that cause BOOP. The histological description of BOOP goes back to as far as 1901, when Lange[13] reported 2 patients using the term "bronchiolitis obliterans". Later, similar cases were described but given different names, for example, bronchiolitis interstitial pneumonia by Leibow and Carrington,[14] and cryptogenic organizing pneumonia (COP) by Davison et al.[15] However, BOOP was recognized as a distinct clinical entity in 1985, when Epler et al[1] reported 57 cases of BOOP after analysis of 2500 reports of open lung biopsy. This classic study and other subsequent reports emphasized the need to differentiate this syndrome from other types of lung pathology with different prognoses, such as idiopathic pulmonary fibrosis (IPF).

Etiology and associated conditions. Most cases of BOOP are idiopathic (up to 80%) but there is an increasing number of conditions and factors described to be associated with it, particularly infections, connective tissue diseases, and drugs (**Table 1**).[16-99] In Epler's original series 50 of 57 cases (88%) were idiopathic, 5 were associated with connective tissue diseases, and 2 with acute inhalation injury. In a Japanese series,[7] 21 of 29 cases (72%) were idiopathic, 5 were associated with connective tissue disease, 5 had chronic thyroiditis and one had alcoholic liver disease. Lately, Cazzato et al,[100] classified BOOP in a series of 78 patients as idiopathic in 68% and secondary in the remainder (radiotherapy for ductal breast carcinoma 6%, connective tissue disease 6%, drugs 9%, infections 4%, and graft versus host disease in 4%). Over the last few years, there were several reported cases of BOOP in association with other conditions which includes hematopoietic stem cell transplantation, orthotopic liver transplantation, lung transplantation, spice processing exposure, sarcoidosis, Sjogren's syndrome, inflammatory bowel disease, adult T-cell leukemia, and myelodysplastic syndrome. Although these

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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 symptomatic, 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 30-50% 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 cavitary 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.[6] Forced vital capacity is reduced (<80%) in 60% of patients.[3,6] Less common, patients with BOOP may have an obstructive defect with a decreased forced expiratory volume in the first second (FEV_1)/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 [8,100,112,113] 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 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.

Infections	Connective Tissue Diseases	Drugs	Miscellaneous
Viruses	Bechet's disease[7]	Acetabutol[56]	Alcoholic cirrhosis[7]
Herpes virus[16,17]	Mixed connective tissue disease[3]	5-Aminosalicylic acid[57]	Bone marrow transplantation[75]
Human immunodeficiency virus[18-20]	Polyarteritis nodosa[47]	Amiodarone[9,56,58,59]	Common variable immunodefiency syndrome [76]
Influenza virus[21,22]	Polymyalgia rheumatica[48,49]	Amphotericine B[60]	Crohn's disease[77]
Parainfluenza virus[23]	Polymyositis and dermatomyositis[2,50]	Bleomycin[61]	Evans syndrome[78]
Bacteria	Rheumtoid arthritis[2,51]	Bucillamine[62]	Idiopathic thrombocytopenic purpura[79]
Chlamydia pneumoniae[24,25]	Systemic lupus erythematosus[3,52]	Carbamazepine[63]	Leukemia[10,80]
Coxiella burnetii[26,27]	Systemic sclerosis[15,55]	Cephalosporins[9,60]	Liver transplant[81,82]
Legionella pneumophilia[21,28,29-33]	Sjogren syndrome[53,54]	Cocaine[64]	Lung transplant[83]
Mycoplasma pneumoniae[21,28,34]		Gold[9,65]	Myelodysplastic syndrome[84,85]
Nocardia asteroids[35,36]		Interferon[59,66]	Radiation therapy[86-93]
Pseudomonas aeruginosa[16]		L-Trytophan[67]	Renal transplant[94]
Staphylococcus aureus[16]		Methotrexate[60]	Sarcoidosis[95]
Streptococcus group B[38]		Minocycline[68]	Seasonal syndrome with cholestasis[96]
Streptococcus pneumoniae[39-41]		Naproxen[48]	Spice processing[97]
Parasites		Nitrofurantoin[69,70]	Sweet's syndrome[98]
Malaria[42]		Phenytoin[71]	Thyroid disease[99]
Fungi		Sotalol[72]	Ulcerative colitis[57,60]
Cryptococcus neoformans[43]		Sulindac[60]	
Penicillium janthinellum[44]		Sulphamethoxyridazine[60]	
Pneumocystis carinii (in AIDS)[16,45,46]		Sulphasalazine[60]	
		Tacrolimus[73]	
		Ticlopidine[74]	

Table 2 - Clinical and roentgenographic manifestation in different studies*

Variables	Epler et al[1] N=57	Cordier et al[5] N=16	Bellomo et al[109] N=6	Costabel et al[9] N=14	Izumi et al[6] N=34	Kings et al[8]‡ N=112	Cazzato et al[100] N=78
Clinical manifestation							
Fever	28	88	50	71	53	46	63
Influenza-like syndrome	28	88	83	71	NA	39	27
Dyspnea	40	88	83	93	47	58	58
Cough	76	63	100	79	76	72	53
Weight loss	NA	63	35	71	NA	48	13
Crackles	68	75	100	86	79	75	78
Clubbing	0	6	0	0	3	4.5	0
Smoker	24	38	33	21	26	17.8	54
Ex-smoker	30	NA	67	NA	18	22.2	14
Non-smoker	46	NA	0	NA	56	30	32
Chest radiograph							
Diffuse	69	25	33	100†	68	68	80§
Localized	4.8	31	33	NA	NA	NA	NA
Reticulonodular	19	44	0	0	6	Rare	17

* 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.[100] 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)**.[3,12,21] 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.

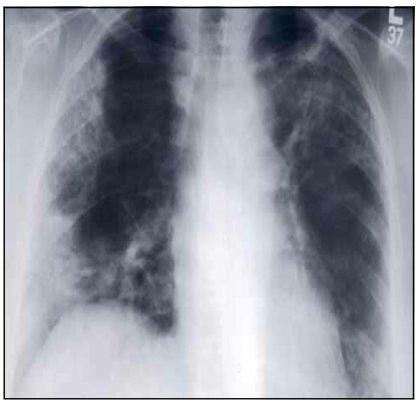

Figure 1 - Chest radiograph showing bilateral pleural based infiltrate typical of bronchiolitis obliterans organizing pneumonia.

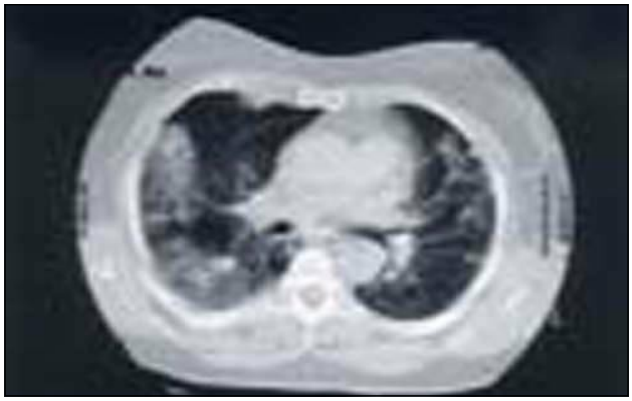

Figure 2 - High resolution computed tomography showing bilateral pleural based infiltrate typical of bronchiolitis obilterans organizing pneumonia.

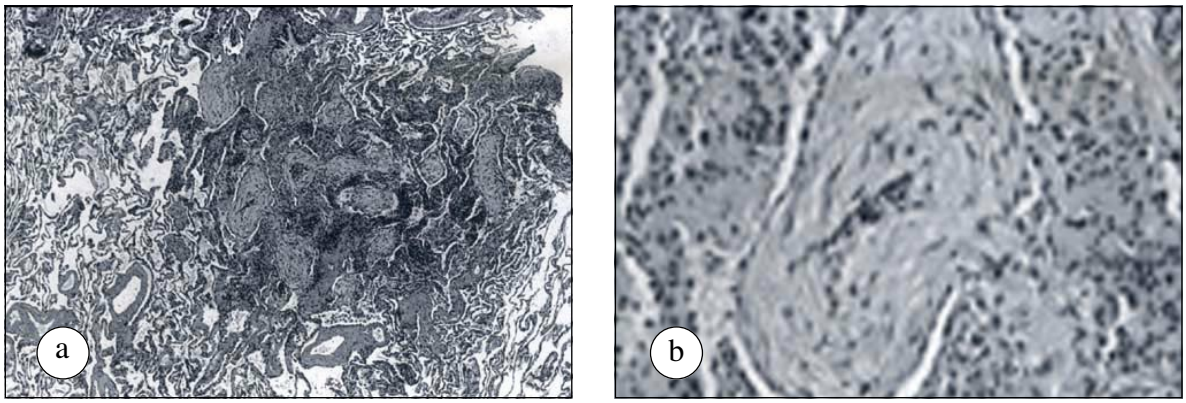

Figure 3 - The picture shows mason body within respiratory bronchiole. Open lung biopsy show focal area of bronchiolitis obliterans organizing pneumonia. **(a)** The lung inbetween is normal. **(b)** High power photomicrograph of bronchiolitis obliterans organizing pneumonia.

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,[115] 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,[116] and 4. 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%).[6,117]

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.[1,2,4-9,104] Approximately 25-30% of patients demonstrate persistent disease and 5% may progress rapidly to respiratory failure and death.[118,119] 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.[100] Most patients who relapse show improvement when therapy is restarted.[8] 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.[120,121] 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.[6] 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.[122,123] 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.[123] 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,[124] 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, pirfenidone, methotrexate, and erythromycin.[125-130] 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,[1,5,6,9,100] and that some patients might even remit spontaneously.[100,104,131] However, there are subgroups in whom progressive disease develops leading to Acute Respiratory Distress Syndrome (ARDS), and die from respiratory failure.[118,119,124,132,133]

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,[1,3,4,117,134] (except for some studies that showed good prognosis in association with rheumatoid arthritis).[7,51,135] 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.[136] 5. Hepatic cholestasis was found to be a risk factor in one study.[136] Relapses do not affect outcome, and prolonged therapy to suppress relapses appears unnecessary.[136]

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 trails are still needed to determine the optimal use of corticosteroids and the potential benefits of other therapeutic agents.

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