# Original Research

## Clinical and Radiologic Distinctions Between Secondary Bronchiolitis Obliterans Organizing Pneumonia and Cryptogenic Organizing Pneumonia

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**BACKGROUND: Bronchiolitis obliterans organizing pneumonia (BOOP) is a distinct pattern of reaction of the lung to injury. It may be idiopathic or secondary to a variety of injuries. The term cryptogenic organizing pneumonia (COP) is used for patients with idiopathic BOOP. In this study we describe clinical and radiologic features of patients with BOOP. METHODS: The medical records of 33 patients with diagnosis of BOOP on surgical lung biopsy over a 10-year time period were reviewed retrospectively. We obtained data on clinical and radiologic manifestations, etiology, and outcome of these patients. RESULTS: Dyspnea was the most common symptom, followed by dry cough and fever. Crackles was the most common physical finding. Mean age at diagnosis of BOOP was 59 years, and 42% were females. The main radiologic manifestation was bilateral patchy consolidation. Most patients had favorable prognosis; however, 17% did not respond to treatment. Female sex was more common in COP than in secondary BOOP ($P = .004$). Patients with COP had longer symptom duration before the diagnosis than secondary BOOP ($P = .01$). Patients with secondary BOOP reported fever more frequently, compared to COP ($P = .005$). Pleural effusion was present in 60% of patients with secondary BOOP, whereas none of the patients with COP had effusion ($P = .004$). CONCLUSIONS: COP and secondary BOOP have diverse clinical and radiologic manifestations. Patients with secondary BOOP are more symptomatic. Both COP and secondary BOOP patients have good prognosis, and most respond to treatment with corticosteroids or by discontinuing the injurious drug.** *Key words: bronchiolitis obliterans organizing pneumonia, cryptogenic organizing pneumonia, interstitial lung disease, drug-induced pneumonitis.* [Respir Care 2009; 54(8):1028–1032. © 2009 Daedalus Enterprises]

### Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP) is a distinct pattern of reaction of the lung to injury. It is characterized by granulation tissue plugs within the lumens of small airways, alveolar ducts, and alveoli. The term "bronchiolitis obliterans" was first used by Lange[1] in 1901.

BOOP may be idiopathic or secondary to a variety of injuries. When idiopathic it is called cryptogenic organizing pneumonia (COP), a term first used by Davison et al[2] in 1983. In 1985 Epler et al[3] described a group of 50 patients with "bronchiolitis obliterans organizing pneumonia" of unknown etiology with a good prognosis. When a clear clinical risk factor for lung injury is identified in a patient with BOOP, the diagnosis is termed secondary BOOP.[4]

SEE THE RELATED EDITORIAL ON PAGE 1020

The purpose of this retrospective study is to describe the clinical presentation, etiology, radiologic manifestation, di-

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agnostic evaluation, and response to treatment of 33 patients with BOOP confirmed via lung biopsy. We hypothesized that there are clinical and radiologic features that can help distinguish COP from secondary BOOP.

## Methods

We retrospectively identified all patients with diagnosis of BOOP on lung biopsy from January 1, 1998, to January 1, 2008, from our tertiary-care referral hospital. An experienced pulmonary pathologist confirmed the pathology diagnosis of BOOP in all lung specimens. The pulmonary tissue for review was obtained via open-lung biopsy or transbronchial lung biopsy. The series included patients with diagnosis of either COP or secondary BOOP, based upon the absence or presence of established clinical causes.

We reviewed the medical records of these patients to obtain demographic data, symptoms at presentation, pulmonary function tests, plain chest radiographs, computed tomograms (CTs), response to treatment, and etiology of BOOP. We defined fever if the admission temperature was more than 100.4 °F. Our local institutional review board approved the study.

The pulmonary function results and CTs were available for 21 of the 33 patients. CT was performed with a GE 9800 or a Philips MX 800 scanner, using 10-mm collimation scans. The 1.5-mm scans were reconstructed using a high-spatial-frequency algorithm (high-resolution CT). All scans were performed at end-inspiration. The scans were photographed at window and level settings designed to optimize the display of lung parenchyma (level −600 to −700, width 1,000–2,000 H) and mediastinum (level 30–50, width 350–500 H).

An experienced chest radiologist reviewed all the scans, blinded to the clinical information of patients. The radiologist also assessed the patterns and distribution of pulmonary abnormalities on CTs. The abnormalities were classified as consolidation, ground-glass attenuation, and nodules. Other features, including migratory sign, pleural effusion, mediastinal lymphadenopathy, reverse halo sign, and septal lines, were also assessed. The Fleischner Society's glossary[5] for defining thoracic radiologic abnormalities was used.

The pulmonary function results were interpreted as being normal, restrictive, obstructive, or mixed pattern, according to American Thoracic Society criteria.[6] We reported the diffusion capacity as being decreased if the diffusing capacity of the lung for carbon monoxide was less than 75% of predicted.

### Statistical Analysis

We analyzed data with statistics software (Stata 10, StataCorp, College Station, Texas). We report continuous variables as mean ± standard deviation. We used the Wilcoxon rank-sum (Mann-Whitney) test and Fisher's exact test to compare continuous and categorical variables, respectively. We considered a $P$ value of less than .05 statistically significant.

## Results

### Clinical and Radiologic Manifestations of Bronchiolitis Obliterans Organizing Pneumonia

We identified 33 patients with the pathological diagnosis of BOOP over the last 10 years (Table 1). The diagnosis of BOOP was established via open-lung biopsy in 29 patients and transbronchial lung biopsy in 4 patients. There were 18 patients with COP and 15 with secondary BOOP, based on the clinical history. Patients were diagnosed with COP if the physician could not find any etiology for BOOP.[4] Among 15 patients with secondary BOOP, 3 patients had BOOP secondary to radiation treatment for lung cancer. Seven patients had chemotherapeutic drugs as an underlying cause. There were 2 patients with systemic lupus erythematous, and one each with ulcerative colitis, amiodarone, and cocaine abuse.

The overall mean age was 59 ± 14 y. There were 19 males and 14 females. Dyspnea was the most common symptom (67%), followed by cough (60%) and fever (45%). The cough was mostly dry and without hemoptysis. In 21% of cases the patients were asymptomatic. The mean duration of symptoms before diagnosis was 4.5 ± 3.6 weeks. Few patients (6%) were current smokers at the time the diagnosis was established.

Pulmonary function test results were available for 21 of the 33 patients (Table 2). Diffusion impairment was the most common finding, seen in 50% of the patients. The lung-function study was normal in 43%, obstructive in 24%, restrictive in 19% and mixed in 14% of the patients.

On chest radiology, consolidation (67%) was the most common radiologic finding, followed by nodule (33%) and ground-glass opacity (29%). Ground-glass opacity was always accompanied by consolidation. Migratory sign was seen in 24% of patients. None of the patients had reverse-halo sign (Table 3).

### Distinguishing Features of Cryptogenic Organizing Pneumonia and Secondary Bronchiolitis Obliterans Organizing Pneumonia

Patients with COP tended to be older than those with secondary BOOP, although the difference did not reach statistical significance (63 ± 3 y vs 54 ± 4 y, respectively, $P = .07$). Female sex was more common in COP than in secondary BOOP (67% vs 13%, $P = .004$).

Patients with COP had longer symptom duration before the diagnosis than patients with secondary BOOP

Table 1. Clinical Profiles of 33 Patients With Bronchiolitis Obliterans Organizing Pneumonia

| Variable | Total ($n$ = 33) | COP ($n$ = 18) | Secondary BOOP ($n$ = 15) | $P$ |
|---|---|---|---|---|
| Age (mean ± SD y) | 59 ± 14 | 63 ± 3 | 54 ± 4 | .07 |
| Male* | 19 (58) | 6 (33) | 13 (87) | .004 |
| Smoking history | | | | >.99 |
| Non-smoker | 15 (45) | 8 (44) | 7 (47) | |
| Former smoker | 16 (48) | 9 (50) | 7 (47) | |
| Current smoker | 2 (6) | 1 (6) | 1 (7) | |
| Incidental finding (or asymptomatic) | 7 (21) | 6 (33) | 1 (7) | .09 |
| Dyspnea | 22 (67) | 12 (67) | 10 (67) | >.99 |
| Cough | 20 (61) | 10 (56) | 10 (67) | .72 |
| Sputum | 2 (6) | 1 (6) | 1 (7) | >.99 |
| Fever | 15 (45) | 4 (22) | 11 (73) | .005 |
| Hemoptysis | 1 (3) | 0 (0) | 1 (7) | .45 |
| Chest pain | 2 (6) | 0 (0) | 2 (13) | .19 |
| Crackles | 19 (58) | 11 (61) | 8 (53) | .73 |
| Wheeze | 0 | 0 | 0 | NA |
| Duration of symptoms (mean ± SD wk) ($n$ = 26) | 4.5 ± 3.6 | 6.2 ± 1.0 | 2.8 ± 0.7 | .01 |

Values are expressed as $n$ (%) unless otherwise indicated.
* Because of rounding, percent values may not sum to 100.
COP = cryptogenic organizing pneumonia
BOOP = bronchiolitis obliterans organizing pneumonia
NA = not applicable

Table 2. Pulmonary Function Test Results From 21 Patients With Bronchiolitis Obliterans Organizing Pneumonia

| | Total ($n$ = 21) | COP ($n$ = 13) | Secondary BOOP ($n$ = 8) | $P$ |
|---|---|---|---|---|
| $FEV_1$ (L) | 2.35 ± 1.02 | 2.22 ± 0.91 | 2.57 ± 1.22 | .43 |
| $FEV_1$ (% predicted) | 81 ± 21 | 82 ± 19 | 89 ± 25 | .87 |
| FVC (L) | 3.18 ± 1.21 | 3.03 ± 1.18 | 3.43 ± 1.32 | .43 |
| FVC (% predicted) | 89 ± 17 | 90 ± 17 | 88 ± 19 | .93 |
| $FEV_1$/FVC | 0.73 ± 0.10 | 0.73 ± 0.10 | 0.71 ± 0.11 | .80 |
| TLC (L) | 5.44 ± 2.11 | 5.26 ± 2.02 | 5.72 ± 2.54 | .83 |
| TLC (% predicted) | 93 ± 20 | 96 ± 20 | 88 ± 22 | .52 |
| $D_{LCO}$ (mL/min/mm Hg) | 17 ± 7 | 17 ± 7 | 17 ± 9 | .89 |
| $D_{LCO}$ (% predicted) | 64 ± 21 | 69 ± 22 | 55 ± 17 | .24 |

Values are expressed as mean ± SD.
COP = cryptogenic organizing pneumonia
BOOP = bronchiolitis obliterans organizing pneumonia
$FEV_1$ = forced expiratory volume in the first second
FVC = forced vital capacity
TLC = total lung capacity
$D_{LCO}$ = diffusing capacity of the lung for carbon monoxide

(6.2 ± 1.0 wk vs 2.8 ± 0.7 wk, respectively, $P$ = .01). Fever was more common in patients with secondary BOOP, compared to COP (73% vs 22%, $P$ = .005). Asymptomatic presentation was more common in patients with COP, compared to secondary BOOP, although the difference did not reach statistical significance (33% vs 7%, $P$ = .09).

Pleural effusion was seen in 60% of patients with secondary BOOP, compared to none of the patients with COP ($P$ = .004). Effusions, when present, were generally small in size, and never massive.

## Treatment and Outcome

Seven patients had a solitary pulmonary nodule, which was resected. Twelve patients received treatment with corticosteroids; 10 had good clinical response while 2 (17%)

Table 3. Radiologic Manifestations in 21 Patients With Bronchiolitis Obliterans Organizing Pneumonia

| | Total ($n$ = 21) | COP ($n$ = 11) | Secondary BOOP ($n$ = 10) | $P$ |
|---|---|---|---|---|
| Consolidation | 14 (67) | 6 (54) | 8 (80) | .36 |
| Ground-glass opacity | 6 (29) | 2 (18) | 4 (40) | .36 |
| Nodule | 7 (33) | 5 (45) | 2 (20) | .36 |
| Migratory sign | 5 (24) | 1 (9) | 4 (40) | .15 |
| Pleural effusion | 6 (29) | 0 (0) | 6 (60) | .004 |
| Septal lines | 3 (14) | 2 (18) | 1 (10) | >.99 |
| Reverse-halo sign | 0 (0) | 0 (0) | 0 (0) | NA |

Values are expressed as $n$ (%).
COP = cryptogenic organizing pneumonia
BOOP = bronchiolitis obliterans organizing pneumonia
NA = not applicable

did not respond. One of the patients who received steroid without clinical response had COP, and the addition of cyclophosphamide to the treatment regimen was not beneficial. The other patient who failed treatment with steroid had BOOP secondary to chemotherapy, and died of acute respiratory failure. We had follow-up information on these patients till their discharge from the hospital. For 14 patients treatment was not deemed necessary, and they were discharged home.

## Discussion

BOOP is a distinct histopathological entity that is characterized by granulation tissue plugs (Masson bodies) within the lumens of small airways, alveolar ducts, and alveoli. When idiopathic, the term COP is used.[7] In our series of 33 patients the etiology or underlying condition predisposing to BOOP was not known in 54% of patients.

BOOP may occur secondary to a variety of injuries, including viral infection,[8,9] inhalation of toxic gases,[10,11] drugs,[12] connective-tissue disorder,[13-16] radiation therapy,[17] cocaine,[18] inflammatory bowel disease,[19-21] and human immunodeficiency virus infection.[22,23] In our series we identified cases of BOOP secondary to radiation, chemotherapy, systemic lupus erythematous, cocaine, amiodarone, and ulcerative colitis.

The clinical features of BOOP have been described previously.[24-29] It is characterized by flu-like illness, dry cough, and dyspnea. We noticed that patients with COP were older and less symptomatic than patients with secondary BOOP. COP was more common in females, and patients with COP had longer symptom duration before the diagnosis was established. It is possible that the presence of important underlying disease in patients with secondary BOOP prompted the physicians to be more urgent in establishing the diagnosis.

The main radiologic picture of BOOP is patchy consolidation, with or without ground-glass haziness, and this pattern has been described by several authors.[30-33] This was the most common radiologic manifestation found in our study, and was noticed in 67%. We identified 33% of patients with incidental nodule on chest radiology. Recently, Maldonado et al[34] described clinical and radiologic manifestations in 26 patients with focal organizing pneumonia. Migratory sign,[35,36] which refers to pulmonary opacities that clear and return in a different location, was seen in 24% of our patients. Interestingly 60% of our patients with secondary BOOP had pleural effusion, compared to none of those with COP. This may be explained by the fact that patients with secondary BOOP and COP have different histopathologic response to the injury.[37] Kim et al[38] have reported reverse-halo sign in 19% of patients with COP. In our series we did not find any patient with reverse-halo sign.

Earlier studies on patients with BOOP described a predominantly restrictive abnormality in lung-function study. We found normal, obstructive, restrictive, and mixed defects in our group of patients. Obstructive ventilatory defect was common in these patients, and it may be due to a large proportion of patients with history of smoking.

The diagnosis of BOOP can be made by obtaining pulmonary tissue, either via open-lung biopsy or transbronchial lung biopsy. Open-lung biopsy remains the accepted standard for the diagnosis, although a good specimen obtained via transbronchial lung biopsy may be sufficient for making the diagnosis.[39] We established the diagnosis of BOOP via transbronchial lung biopsy in 4 patients. In all 4 patients the transbronchial lung-biopsy specimen produced evidence of both organizing pneumonia and granulation tissue plugs in the lumens of small airways and in alveoli.

The prognosis of both COP and secondary BOOP is good. In our series more than 80% of patients responded to corticosteroids. The in-patient mortality was 3% in our group. There were 2 patients who did not respond to corticosteroids. In one patient with COP the addition of cyclophosphamide was not beneficial.

Our study has some limitations. The sample size was small; however, this is a common drawback of studies of rare diseases. Because it was a retrospective study, we were not able to obtain lung-function study and radiologic information on all patients.

## Conclusions

BOOP is a non-specific pattern of reparative response of lung to the injury. It may be idiopathic or secondary to a variety of injuries. It is an uncommon condition but should be considered in the differential diagnosis of patients with bilateral patchy consolidation. Patients with

COP were mostly female and less symptomatic, compared to patients with secondary BOOP. Consolidation and ground-glass haziness were typical radiologic manifestations, and patients with secondary BOOP may also have pleural effusion. Both COP and secondary BOOP were corticosteroid responsive with a good prognosis.

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