Cryptogenic Organizing Pneumonitis*  
The North American Experience  
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Idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP) or cryptogenic organizing pneumonitis (COP) is a specific clinicopathologic syndrome of unknown etiology. Since the histopathologic lesions present in this syndrome can be identified in variable degrees in other disease settings (usually much less extensive and severe), we believe that the term cryptogenic organizing pneumonitis best conveys the fact that the syndrome described in this review is a distinct entity. Recognition of COP has increased since the description of Grinblat and coworkers of 2 patients with organizing pneumonia and steroid responsiveness. Subsequent larger series by Davison and associates from England and Epler and coworkers from North America served to highlight the characteristic clinical course and suggested that COP was a distinct entity with features of a pneumonia rather than a primary airway disorder. Importantly, this syndrome can and should be distinguished from other causes of lung fibrosis, such as idiopathic pulmonary fibrosis and also from bronchiolitis obliterans associated with irreversible obstructive lung disease.4

Unlike most causes of pulmonary fibrosis, patients with COP have a more benign course with a good prognosis, especially in response to treatment with corticosteroids. Thus, information that can help clinicians make the diagnosis of COP is important. This review focuses on our current understanding of COP in adults describing the keys to diagnosis and management, especially those features useful in distinguishing it from idiopathic pulmonary fibrosis (IPF).

METHODS

Data Identification and Study Selection

We reviewed 4 major published reports of patients with COP from centers in North America. In addition, patients with COP studied at our institution were included in the patient population (unpublished data). These studies were selected because they included 5 or more subjects with the diagnosis confirmed by lung biopsy specimen. These works were reviewed critically for information on the clinical, physiologic, roentgenographic, and pathologic findings of COP.

Data Extraction

The 4 published reports contained 94 subjects, and 18 consecutive patients with COP studied at our institution were also included. Several clinical variables, when available, were extracted from each of the populations reported. Each variable was analyzed to provide an accurate composite description of COP. In addition, these data were compared with similar findings from a large series of patients with IPF.

RESULTS

Patient Characteristics

Cryptogenic Organizing Pneumonitis: The diagnosis of COP was established on the basis of a compatible history, physical examination, chest roentgenogram, pulmonary physiologic evaluation, and a confirmatory lung biopsy specimen. The mean age of the 112 subjects was 58 years (range, 21 to 80 years). There were 52 women and 60 men. The smoking history was available in 79 subjects: 34 were never smokers, 20 were current smokers, and 25 were ex-smokers.

Idiopathic Pulmonary Fibrosis: The clinical findings in the patients with COP were compared with those of 59 patients with IPF. The diagnosis of IPF was established on the basis of a compatible history, physical examination, chest roentgenogram, pulmonary physiologic evaluation, and a confirmatory open lung biopsy specimen. The mean age of the 59 subjects was 52 years (range, 29 to 77 years). There were 20 women and 39 men. The smoking history was available in 39 subjects of whom 16 were never smokers and 23 were current smokers or ex-smokers.

Clinical Manifestations

The incidence of COP was the same for both men and women. Interestingly, the age range for patients with COP was identical to that for patients with IPF. There were similar numbers of current or ex-smokers compared with never smokers in patients with COP. The history of cigarette smoking was similar in patients with COP and IPF. The duration of illness prior to lung biopsy is shown in Figure 1. Patients with COP have a consistently shorter duration of illness (mean, 3.6 months) compared with patients with IPF (23.8 months) (Fig 1A). In fact, 78% of patients with COP have a duration of illness of less than 3 months. In contrast, 76% of patients with IPF have a duration of symptoms prior to diagnosis of greater than 3 months (Fig 1B).

As can be seen in Figure 2A, cough, usually persistent and nonproductive, and breathlessness with exertion were the most common presenting symptoms. Interestingly, a flu-like illness appeared to herald the onset of COP in two fifths of the patients. In patients with IPF from our center, a history of a flu-like illness was only elicited in 20% of the subjects. Malaise, fever, and weight loss (of approximately 2.25 to 4.5 kg) were common complaints in patients with COP (Fig 2B).

The physical examination revealed dry crackles in 75% of the patients with COP (Fig 2B). This was rarely associated with wheezing. Finger clubbing was present in only 4.5% of

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patients with COP and 29% of the patients with IPF. In 22% of the patients with COP (n = 88), results of the physical examination were normal.

**Pulmonary Function Testing**

Lung function studies were available in 69 patients prior to diagnosis and treatment (Fig 3). These studies revealed a mild to moderate restrictive defect in 53% of the patients with COP (n = 59). An obstructive defect (FEV1/FVC ratio less than 70%) was found in 28% of subjects with COP (n = 69). In the subset of patients from our group that had an obstructive defect, all were current or former smokers. Occasionally lung function was normal; 4 of the 18 patients studied by our group had normal results of pulmonary function tests. We found that as a group, patients with COP had spirometric and lung volume abnormalities similar to those of patients with IPF.

The diffusing capacity (Dco) was reduced (<80% of predicted) in 75% of patients with COP compared with 91% of patients with IPF. In general, the reduction in Dco in patients with COP was not as great as that found in patients with IPF (Fig 3). Resting and exercise arterial hypoxemia is an almost universal abnormality in patients with COP. Thirty-four of the 40 patients that had arterial blood gases obtained at rest demonstrated a P(A-a)O2 gradient of >20 mm Hg. Patients with IPF had less severe alterations in P(A-a)O2 gradients at rest with only 46% of subjects having a P(A-a)O2 gradient greater than 20 mm Hg at rest. Both groups showed significant abnormalities in gas exchange with exercise.

We performed pressure-volume studies in 12 patients with COP. In these subjects, the pressure-volume curve was shifted downward and to the right consistent with a stiff noncompliant lung (Fig 4A). The maximal transpulmonary

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P(A-a)O_2 > 20 \text{ mmHg}
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Dco < 80\%
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FEV1/FVC < 70\%
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TLC < 80\%
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**Figure 3.** Physiologic findings in patients with COP. The total lung capacity (TLC, n = 59), ratio of forced expired volume in 1 s to forced vital capacity (FEV1/FVC, n = 68), and the diffusing capacity (Dco, n = 53) are indicated as percentages of predicted values. The difference between alveolar and arterial oxygen pressure (P(A-a)O2) at rest is shown in millimeters of mercury, 20 mm Hg being the upper limits of normal.
COP, Cryptogenic 20

wherever, present regular distinctly only COP, increased (maximum pressure TLC) similar H50/L The coefficient of compliance, with volume constant increased inspiration to TLC 3 times prior to the measurement of the volume-pressure relationship. A (upper). Relationship of the static deflation volume and pressure in a patient with COP compared with a patient with IPF. The percent predicted TLC is plotted against the static transpulmonary pressure (cm H2O) for each patient. In general, the correlation, maximum static transpulmonary pressure, and the coefficient of retraction (the maximum transpulmonary pressure to TLC) tend to correlate with the extent of parenchymal involvement of inflammation and fibrosis. B (lower). Coefficient of elastic recoil. The maximal transpulmonary pressure and the coefficient of elastic recoil (maximum transpulmonary pressure/total lung capacity) was increased in the COP group (normal, 2.5 to 8.5).

pressure was increased and the coefficient of elastic recoil (maximum transpulmonary pressure/total lung capacity) was increased in the COP group (Fig 4B). In 6 patients with COP, the coefficient of retraction was greater than 12 cm H2O/L (normal, 2.5 to 8.5).

Roentgenographic Manifestations

The roentgenographic manifestations of COP are described elsewhere in this monograph and will be described only briefly herein. Bilateral, diffuse alveolar opacities in the presence of normal lung volume constituted the characteristic roentgenographic appearance in patients with COP. This pattern was present in 76 of the 100 subjects where the roentgenographic appearance was detailed. A distinctly peripheral distribution to the infiltrates, very similar to that thought to be “virtually pathognomonic” for chronic eosinophilic pneumonia, is commonly seen. Irregular linear or nodular interstitial infiltrates were rarely present as the only roentgenographic manifestation. However, this latter pattern was seen in 36% of the patients with COP. Patients with IPF did not demonstrate alveolar opacities; 100% of subjects with IPF demonstrated diffuse, small, linear, or nodular opacities in the lower lung zones, usually in the presence of reduced lung volumes. Honeycombing was seen occasionally at presentation in patients with IPF but was rarely seen in patients with COP and only as a late manifestation in the few patients with progressive disease. Other roentgenographic abnormalities, such as pleural effusion, pleural thickening, hyperinflation, and cavities occurred rarely in subjects with COP. Chandler et al found no direct correlation between the roentgenographic appearance and the histologic features found at lung biopsy.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) studies have been reported in only a few subjects with COP. We have obtained BAL in 11 subjects prior to diagnosis and treatment. The percentage of instilled fluid recovered in the lavages of patients with COP and IPF was lower than that from the healthy volunteers (HV) (Fig 5A). However, the total cells recovered was greater in patients with COP and IPF compared with HV (Fig 5B). The proportion of macrophages was lower in both patient groups compared with HV. The BAL lymphocytes, neutrophils, and eosinophils were higher in patients with both COP and IFP compared with normal subjects (Fig 6). The patients with COP tended to have higher lymphocyte counts than those patients with IPF.

Diagnosis

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6. Bronchialwular lavage cellular findings in COP compared with IPF. A (top). Lymphocytes. The percentage of cells that were lymphocytes was increased in both groups compared with healthy volunteers. The patients with COP tended to have higher lymphocyte counts than those patients with IPF. B (center). Neutrophils. The proportion of neutrophils was higher in both COP and IPF compared with normal subjects. COP. The proportion of eosinophils was higher in both COP and IPF compared with normal subjects.

COP, other disorders may present with many of the same clinical features, such as hypersensitivity pneumonitis, chronic eosinophilic pneumonia, infection, drug reaction, or connective tissue disorder. Hence, histopathologic analysis, as was performed in all cases in the reports reviewed herein, is imperative to diagnose the classic histologic features. Importantly, the diagnosis of COP depends on both the clinical setting and finding the characteristic pathologic features of the disease. Specific comments and description of the histopathologic changes of COP are discussed elsewhere in this monograph by Colby and have been reported previously by others.5,10-12

Of importance, ample lung tissue must be carefully reviewed to rule out other diseases, especially hypersensitivity pneumonitis or chronic eosinophilic pneumonia. Therefore, an open lung biopsy is recommended to confirm the diagnosis. Transbronchial lung biopsy specimens generally do not provide an adequate sample to definitively confirm BOOP and rule out other disorders. The histologic features of BOOP can be seen in a number of diagnoses.8

Also, it is important that the biopsy specimens be reviewed by an experienced pathologist who has been given adequate clinical information to guide the search for the specific lesions/patterns that support the diagnosis. Once the characteristic histologic lesions are confirmed, the clinician must ensure that a thorough search has been performed to rule out the many possible causes of BOOP—the clinicopathologic syndrome of COP is a diagnosis of exclusion.

Treatment Outcome and Prognosis

The follow-up information on the patients whose cases are reported by these groups was incomplete since these were retrospective studies. Nevertheless, follow-up information was available on 96 subjects with COP (Fig 7). Corticosteroid therapy was by far the most common treatment instituted in these patients. It resulted in clinical recovery, usually with complete clinical and physiologic improvement and normalization of the chest roentgenogram in 63% of the patients. Thirty patients had persistent disease. In general, it was stated that clinical improvement was rapid, ie, within several days or a few weeks, and was quite dramatic in some patients. In the study by Epler and colleagues,4 one third of the patients who had an initial improvement in response to corticosteroid treatment relapsed when the corticosteroid therapy was withdrawn after 1 to 3 months. All improved when retreated with corticosteroids. Spontaneous improvement appears to occur over 3 to 6 months in some patients.3

It has been suggested that patients with airspace opacities on chest roentgenogram have a much better outcome than those with interstitial opacities.5,6,11 Most of the patients in the study of Katzenstein et al6 had complete resolution of disease and only 1 of their patients with alveolar opacities died of progressive disease. However, 6 of the 9 patients with interstitial opacities had persistent roentgenographic abnormalities and 2 died of progressive disease. Interestingly, the studies of both Epler and coworkers4 and Katzenstein and colleagues6 suggested that patients who had an underlying connective tissue disease were more likely to have persistent and often progressive disease.

The overall prognosis of COP is much better than that of
IPF. More patients with IPF who received corticosteroids died of respiratory disease. Of the cases reviewed in this study, 55% of the patients with IPF died during the follow-up period compared with 12% of the patients with COP (Fig 7).

SUMMARY

Cryptogenic organizing pneumonitis is a clinical and pathologic syndrome characterized by a "pneumonia-like" illness with excessive proliferation of granulation tissue within small airways and alveolar ducts associated with chronic inflammation in the surrounding alveoli. The duration of illness prior to lung biopsy is short, usually less than 2 months, and it is markedly different from that of IPF. Interestingly, unlike in IPF where the patient has difficulty remembering the exact onset of symptoms, patients with COP are frequently very specific about the timing of their disease onset. This is because the disease onset is recent and is often dramatic with the development of a severe flu-like illness, ie, cough, fever, malaise, fatigue, and weight loss. Inspiratory crackles are frequently present on chest examination. Pulmonary function is usually impaired with a restrictive defect being most common. Gas exchange abnormalities are extremely common with a reduction in Dco and resting hypoxemia being almost universal findings. The roentgenographic manifestations are quite distinctive with a pattern of bilateral, diffuse but inhomogeneous, ground-glass or alveolar opacities being present in the majority of the cases. Bronchoalveolar lavage findings are nonspecific but usually reveal a lymphocytosis.

The response to corticosteroid treatment is quite favorable and death from progressive disease is uncommon in COP, especially if treatment is instituted early in the course of the disease. In our experience, the cases with the worse prognosis are those associated with another disease process, in particular, connective tissue disorders like rheumatoid arthritis. In fact, these patients are prone to develop a rapidly progressive form of BOOP with a clinical course similar to the "Hamman-Rich syndrome." The recurrences are relatively frequent, consequently, withdrawal of treatment should be done with extreme caution.

Corticosteroids have been the conventional initial treatment of COP, although to our knowledge, there are no controlled clinical trials to support its use. Antibiotics are not effective in treating this syndrome. Thus, based solely on our experience and that of others, we believe that high-dose corticosteroid therapy should be used to treat COP, usually initiated with 1 to 1.5 mg/kg/day (using ideal body weight) not to exceed 100 mg/day. Prednisone is given as a single oral dose in the morning. We recommended maintaining this dose for 4 to 8 weeks. If the patient's condition is stable or improved, the prednisone dosage is gradually tapered to 0.5 to 1 mg/kg/day (using ideal body weight) for the ensuing 4 to 6 weeks. If the patient's condition has deteriorated despite the corticosteroid therapy, a cytotoxic agent is considered while generally maintaining corticosteroid therapy if tolerated. After 3 to 6 months of corticosteroid therapy, if the patient's condition remains stable or improved, the prednisone therapy is gradually tapered to zero. The patient should be followed up routinely, probably every 6 to 8 weeks during the first year and therapy should be reinstituted aggressively at the sign of any recurrence.

High-dose parenteral corticosteroid therapy has been recommended as the initial treatment in patients with rapidly progressive severe courses of COP. Methylprednisolone, 250 mg every 6 h intravenously, has been used in an attempt to suppress the activity of disease as soon as possible. We recommend that this treatment be given for 3 to 5 days to see if it initiates a response, primarily a reduction in symptoms, clearing of the alveolar opacities, and improvement in gas exchange. Although therapy with corticosteroids is usually well-tolerated by patients, side effects are common. Some patients develop side effects of corticosteroids more readily than others at equivalent doses. Therefore, prevention and careful management of the many potential side effects of this therapy are necessary.

We have used cyclophosphamide (Cytoxan) to treat patients with COP who have progressive disease despite adequate corticosteroid therapy. Cyclophosphamide is usually administered in a daily oral dose. The recommended dose is approximately 2 mg/kg/day, although the optimal dose in COP is unknown. We usually start at 50 mg daily and slowly increase the dose over 2 to 4 weeks. We do not recommend exceeding 200 mg/day. A trial of at least 3 to 6 months is needed to ensure an adequate opportunity for clinical response. Hematologic alterations are common side effects of cyclophosphamide therapy and frequently require dose adjustment—the total white blood cell count should be maintained above 4,000. Leukopenia is the most commonly reported hematologic toxic reaction, with anemia and thrombocytopenia noted less often. In some cases, the hematologic effects of cyclophosphamide may persist for several months despite discontinuance of the drug therapy. Urologic complications of hemorrhagic cystitis and carcinoma of the bladder are known, although these are thought to be less common in the dose range used in COP as compared with the higher dosages recommended in chemotherapy regimens. Other complications are possible and should be addressed appropriately if they occur.

That COP is a specific disease appears certain to us. However, without better understanding of the etiology and pathogenesis, we cannot be certain where and how COP fits into the spectrum of diffuse lung diseases. Familiarity with the clinical and histopathologic features outlined above should increase the physician's ability to recognize, diagnose, and manage COP.

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