Idiopathic Organizing Pneumonia: A Relapsing Disease

19 Years of Experience in a Hospital Setting

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Key Words

Bronchiolitis obliterans organizing pneumonia · Cryptogenic organizing pneumonia · Interstitial lung disease · Multifocal opacities · Steroid treatment

Abstract

Background: Although organizing pneumonia (OP) is a common pathological finding, studies including a substantial number of patients with idiopathic forms from a unique center and a long follow-up are rare. **Objectives:** To determine patients with cryptogenic forms of organizing pneumonia (COP), in order to characterize their clinical course, to identify predictive factors for relapse and to assess their effect on outcome. **Methods:** For a 19-year period, all histopathological reports from a community teaching hospital were reviewed, and OP was found in 210 lung specimens belonging to 197 patients. **Results:** Thirty-three (17%) patients presented cryptogenic forms and 32 of them (97%) responded to steroid therapy. At follow-up, 14 patients presented no relapses (no-relapse group, NR) and 18 (56%) presented relapses (relapsing group, RG) that resolved with ulterior treatment. Multifocal opacities on chest X-ray (RG 83% vs. NR 36%, $p = 0.02$) appeared to be a predictor for relapse. Patients with relapses showed a shorter time span to chest X-ray normalization (RG 8 ± 8 weeks vs. NR 13 ± 9 weeks, $p = 0.09$) that became significant in patients with 3 or more relapses (multiple-relapse group, MR, 4 ± 2 weeks vs. NR 13 ± 9 weeks, $p < 0.04$). Although the initial prednisone dose was

similar in patients with relapsing forms, its maintenance was shorter than in patients without relapses, showing a trend to significance (RG 4 ± 3 weeks, NR 7 ± 6 weeks, $p = 0.09$). Lower levels of lactate dehydrogenase and γ -glutamyltransferase, although always within the normal range, were found in patients with relapsing forms. **Conclusion:** COP is a specific but infrequent form of OP with a good response to steroid therapy. Relapses are frequent and typical characteristics of COP which resolved with ulterior treatment. Multifocal opacities on chest X-ray and a shorter maintenance of the initial steroid dose may increase the risk of relapse.

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Abbreviations used in this paper

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BOOP	bronchiolitis obliterans organizing pneumonia
COP	cryptogenic organizing pneumonia
CT	computed tomography
ESR	erythrocyte sedimentation rate
GGT	γ -glutamyltransferase
LDH	lactate dehydrogenase
MR	multiple-relapse subgroup
NR	no-relapse group
OP	organizing pneumonia
RG	relapsing group

Introduction

Cryptogenic organizing pneumonia (COP) is a specific clinical and pathological entity first described by Davison et al. [1] in 1983 and in detail in 1985 by Epler et al. [2] as bronchiolitis obliterans organizing pneumonia (BOOP). The main clinical features include subacute onset of cough, fever, dyspnea, sparse crackles on auscultation and multifocal alveolar infiltrates on chest imaging [3–8]. Hemoptysis and multiple cavitory nodules are very rare [9]. BOOP can exhibit specific computed tomography (CT) features with regard to the crescentic or ring-shaped opacities with a central ground-glass attenuation [10]. The characteristic lesion of COP is proliferative bronchiolitis with the presence of granulation tissue in the distal airspaces. However, histologically, organizing pneumonia (OP) is a common nonspecific pathological response of the lung to injury. The differential diagnosis includes many causal disorders such as infection, post-obstructive pneumonia, fume or toxic gas exposure, collagen vascular diseases, drug injury and diffuse alveolar damage [11–19].

Although it has been stated that in most cases OP is idiopathic, the application of strict diagnosis criteria drastically reduces the number of patients with idiopathic forms. In fact, most series of OP published as COP or idiopathic BOOP include a substantial number of secondary cases [1–2, 6, 20–22].

The aim of the present study was to analyze all patients with a pathological diagnosis of OP seen at a tertiary hospital during a period of 19 years. The main objective was to elucidate its origin and to determine patients without any apparent cause or associated disorder to ascertain its true incidence. Other objectives were to characterize its clinical course, to examine the pattern of relapses, to determine whether relapses affect morbidity and mortality, and to identify possible predictive factors for relapse.

Patients and Methods

Selection of Cases

Using computer-assisted search, all histopathological reports from January 1984 to January 2003 were reviewed, and those explicitly describing the presence of buds of granulation tissue in the distal airspaces based on surgical or transbronchial lung biopsy were selected. The pathological specimens thus identified were revised and medical records reviewed.

Definitions

The following criteria were used to separate the main types of OP:

- *Infectious OP*: Infection was considered the cause when a responsible agent was identified or the presence of polymorphonuclear aggregates, with or without necrosis, was demonstrated on pulmonary tissue, or when the resolution of the disorder was obtained by antibiotic therapy.
- *OP concomitant with Malignancy*: An OP was attributed to a carcinoma or hematological neoplasm in the presence of a physically distinct malignant process.
- *Adjacent OP*: OP in the vicinity of a tumor, bulla or bronchiectasis were included in this group.
- *Postobstructive OP*: Postobstructive OP was defined as OP caused by a functional or non-malignant obstruction.
- *Cryptogenic OP*: This group includes symptomatic patients with areas of consolidation on chest X-ray, OP histology and no recognized underlying cause or associated disorder. Patients undergoing spontaneous or antibiotic resolution were not included in this category.

Relapses

A relapse was defined as the appearance of characteristic new infiltrates on chest imaging, with compatible clinical features, after a complete remission. A histopathological confirmation of COP was not required for the diagnosis of relapse, if typical.

Data Analysis

The following variables were evaluated: sex, age, smoking status, symptoms and signs, erythrocyte sedimentation rate (ESR), C-reactive protein, hemoglobin, blood cell count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyltransferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), rheumatoid factor, antinuclear antibodies, serological assays for *Mycoplasma pneumoniae*, *Chlamydia psittaci*, *Chlamydia* spp., *Chlamydia pneumoniae*, *Legionella pneumophila*, *Coxiella burnetii*, *Rickettsia conori*; adenovirus, respiratory syncytial virus, cytomegalovirus, hepatitis virus, influenza and parainfluenza virus; bacteriological studies, including *Mycobacterium tuberculosis* in sputum and bronchial aspirates, immunological status, drug consumption, chest X-rays, CT scans, pulmonary function testing, arterial blood gases, bronchoalveolar lavage (BAL), medical treatments and outcome. Numerical data were expressed as means $\pm$ SD and compared by two-way analysis of variance and unpaired t test. Proportions were compared by the χ^2 test.

With respect to idiopathic forms, particular emphasis was focused on the delay between first symptoms and diagnosis, chest X-ray changes before the introduction of steroid therapy, daily dose of prednisone at any time of the treatment period, use of immunosuppressant drugs, delays for clinical recovery and chest X-ray clearing, number and timing of relapses, treatment side effects, radiographic and functional sequels, and follow-up time.

Results

Between January 1984 and January 2003, OP was found in 210 lung specimens belonging to 197 patients. Diagnostic histopathological specimens were obtained by transbronchial biopsy in 124 (63%) patients, video-assisted thoracoscopy or open lung biopsy in 15 (8%) patients, sur-

Table 1. A causal classification of the 197 patients with OP

Adjacent	Postinfectious	Idiopathic (COP)	Environmental exposure	OP concomitant with malignancy	Postobstructive	Miscellaneous
57 (29%)	38 (19%)	33 (17%)	15 (8%)	7 (4%)	11 (6%)	36 (18%)
Malignancy (49) Bronchiectasis (5) Bulla (3)	identified infectious agent (19) <i>Pneumocystis jirovecii</i> (4) <i>M. pneumoniae</i> (3) <i>Chlamydia</i> spp. (3) <i>M. tuberculosis</i> (3) <i>L. pneumophila</i> . (2) <i>Streptococcus viridans</i> (2) <i>Pseudomonas aeruginosa</i> (1) <i>Peptostreptococcus</i> (1) no identified infectious agent (19) abscess (3) slow resolving pneumonia (16)	Ardystil ^a (14) chlorine (1)	lymphoma (2) lung cancer (1) prostate cancer (1) multiple myeloma (1) ovarian cancer (1) breast cancer (1)	asthma (9) ABPA (1) intra bronchial foreign body (1)	amiodarone (6) collagen vascular diseases (6) ^b UIP and AIP (5) DAD (3) granulomatous (3) chronic eosinophilic pneumonia (2) hypersensitivity pneumonitis (2) follicular bronchiolitis (2) acquired common variable immunodeficiency (2) inflammatory pseudotumor (1) exogenous lipoid pneumonia (1) Langerhans cell histiocytosis (1) gastroesophageal reflux (1) congenital lobar emphysema (1)	

AIP = Acute interstitial pneumonia; ABPA = allergic bronchopulmonary aspergillosis; DAD = diffuse alveolar damage; UIP = usual interstitial pneumonia.

^a Exposure to acramin FWN.

^b Four cases of rheumatoid arthritis, 1 dermatomyositis and 1 systemic sclerosis.

gical resection in 54 (27%) patients and necropsy in 4 (2%). A causal classification is shown in table 1.

Adjacent OP was the type most frequently encountered (29%). Thirty-three cases of adjacent OP were identified in a prospective cross-sectional study aimed to assess the frequency of OP in patients with resected lung tumors [14]. Idiopathic forms were found in 33 patients (17%), a frequency exceeded by postinfectious (19%) and miscellaneous forms (18%).

COP

Thirty-three patients fulfilled the criteria for COP. The general characteristics of the 33 patients with COP at the time of diagnosis are shown in table 2. The proportion of nonsmokers was significantly higher among women (94 vs. 40%, $p = 0.001$). Serological screening, always with a negative result, was performed in 19 (58%) of the 33 patients considered idiopathic. Cough, breathlessness together with crackles and fever were the most frequent symptoms and signs found at diagnosis. Most patients presented an increased ESR, with a mean of 80 ± 37 mm in the first hour.

Roentgenological Manifestations

Chest X-ray showed multifocal opacities in 21 patients (64%), a solitary opacity in 7 (21%) and a diffuse intersti-

tial infiltrative pattern in 5 (15%; table 2). Before initiation of steroid therapy, the migratory character of the infiltrates could be demonstrated in 4 patients (12%). At diagnosis, chest CT (performed in 25 patients) confirmed the roentgenological pattern observed in plain chest radiography.

Pulmonary Function Tests

Seventeen (52%) patients presented a restrictive spirometric defect (6 mild, 8 moderate and 3 severe); 4 (12%) a combined defect, and 3 (9%), all smokers, a mild obstructive defect. Nine (27%) patients had spirometric tests within the normal range [23]. At diagnosis, the mean PaO_2 of the 27 patients studied was 64 ± 31 mm Hg and the A-a PO_2 gradient was 35 ± 14 mm Hg.

Bronchoalveolar Lavage

BAL was abnormal in the 12 patients in whom this exploration was performed before diagnosis. Two patients showed more than 5% of neutrophils; 3 more than 10% of lymphocytes, and the remaining 7 patients showed an elevated percentage of both types of leukocytes. The mean volume of BAL fluid recovered was 68 ± 19 ml. The total cell count was $19.5 \pm 13.4 \times 10^6$ cells/100 ml⁻¹. The differential count was: $57 \pm 19\%$ macrophages, $16 \pm 14\%$ neutrophils and $28 \pm 21\%$ T lymphocytes.

Fig. 1. Dose of prednisone at the time of the first relapse in 18 patients with COP.

Initial Treatment

Thirty patients (91%) underwent antibiotic therapy during 17 ± 6 days (6–35 days) before the diagnosis without apparent improvement. The mean daily dose of prednisone to treat the initial episode (56 ± 12 mg) was maintained for 5 ± 4 weeks.

Follow-Up

Follow-up was prolonged to January 2004, 12 months after the last patient was included. Mean duration after diagnosis was 54 ± 40 months, with no incident that might put the initial diagnosis of COP into doubt. No patient was lost to follow-up.

Relapses

No relapse occurred in 14 of 32 (44%) patients (NR group), whereas 18 (56%) patients relapsed (relapsing group, RG group); 6 (19%) of them presented 3–8 relapses (multiple-relapse subgroup, MR subgroup). The first relapse occurred within 6 months after the initial episode in 8 (44%) of the 18 patients, and within 1 year in 14 (78%). The mean time to the first relapse was 10 ± 12

Table 2. General characteristics of the 33 patients with COP at the time of diagnosis

Characteristics	Patients
Mean age, years	62 ± 10
Range	41–85
Male sex	45
Current smokers	30
Transbronchial lung biopsy	85
Surgical lung biopsy	15
Mean duration of symptoms before diagnosis, weeks	7 ± 3
Range	3–13
Clinical data	
Cough	88
Fever $>38^{\circ}\text{C}$	76
Breathlessness	58
Chest pain	52
Weight loss $>10\%$	42
Flu-like illness	21
Hemoptysis	12
Crackles	73
Clubbing	9
Serum parameters	
Leukocytes $>11,000/\text{mm}^3$ ^a	45
Neutrophils $>70\%$ ^a	70
ESR $>20/\text{mm}$ 1st h ^a	90
LDH >460 IU/l ^a	10
AST >37 IU/l ^a	10
ALT >41 IU/l ^a	16
GGT >61 IU/l ^a	10
Alkaline phosphatase >258 IU/l ^a	13
Chest X-ray	
Multifocal opacities	64
Solitary opacity	21
Diffuse interstitial infiltrates	15
Migratory character	12
Pleural effusion	6
Cavitary lesion	6

Percentages of patients (except otherwise indicated) are shown.

^a Upper normal serum limit.

months (range 2–54). In the present series, a patient with a progressive form, without evidence of complete remission, was excluded from the analysis.

Treatment at the Time of the First Relapse

Ten of the 18 (56%) RG patients were still on steroid therapy (mean prednisone dose 10 ± 9 mg/day; range 2.5–30 mg/day) when the first relapse occurred. Only 2 patients were on 20 mg/day or more (fig. 1).

Table 3. Comparison of NR and RG groups

	NR n = 14	RG n = 18	p
Multifocal opacities	5 (36%)	15 (83%)	0.02
LDH, IU/l	377 ± 92	295 ± 66	0.01
AST, IU/l	28 ± 17	20 ± 8	0.08
GGT, IU/l	50 ± 33	25 ± 16	0.01
Maintenance of initial prednisone dose, weeks	7 ± 6	4 ± 3	0.09
Chest X-ray normalization, weeks	13 ± 9	8 ± 8	0.09
Total time on steroid treatment, months	13 ± 12	40 ± 41	0.02

Predictors of Relapse

Multifocal opacities on chest X-ray (RG 83% vs. NR 36%, $p = 0.02$) appeared to predict relapse. Lower levels of serum LDH (RG 295 ± 66 vs. NR 377 ± 92 IU/l, $p = 0.01$) and GGT (RG 25 ± 16 vs. NR 50 ± 33 IU/l, $p = 0.01$) were found in patients with relapsing forms, although they were always within the normal range. The remaining laboratory and clinical findings did not show significant differences. Although the initial prednisone dose was similar in both groups, treatment duration was shorter in relapsing patients, but the difference did not reach statistical significance (RG 4 ± 3 weeks, NR 7 ± 6 weeks, $p = 0.09$). The time to chest X-ray normalization was shorter in the RG group (RG 8 ± 8 vs. NR 13 ± 9 weeks, $p = 0.09$) but not statistically significant (table 3).

Patients with multiple relapses showed lower levels of serum LDH (MR 288 ± 31 vs. NR 377 ± 92 IU/l, $p < 0.007$) and a shorter time to chest X-ray normalization compared with patients without relapses (MR 4 ± 2 weeks vs. NR 13 ± 9 weeks, $p < 0.04$). The follow-up of the MR group was longer than in the NR group (MR 95 ± 40 vs. NR 42 ± 37 months, $p < 0.01$).

Effect of Relapses on Pulmonary Function

At the last follow-up, while in remission, no significant differences in spirometry were found between both groups (FVC $91 \pm 19\%$ and FEV₁/FVC $94 \pm 15\%$ of predicted values in NR vs. FVC $93 \pm 18\%$ and FEV₁/FVC $93 \pm 14\%$ in RG).

Treatment of Relapses

All relapses were treated by resuming or increasing steroid treatment. The mean prednisone dose at treatment initiation for the first relapse was 38 ± 19 mg/day, being significantly lower than at initial treatment ($p < 0.001$).

The RG group and predominantly the MR subgroup required longer steroid treatment than the NR group (NR

12 ± 3 ; RG 42 ± 10 , $p < 0.01$, and MR 98 ± 48 months, $p = 0.03$).

Outcome

Twenty-six of the 33 cases are alive and non-symptomatic up to 144 months after diagnosis. However, 2 are still on steroid therapy: an 80-year-old man, with a daily dose of 10 mg of prednisone, 8 years after diagnosis and after 8 relapses, and a 63-year-old woman, with a daily dose of 20 mg of prednisone, 5 years and 8 relapses after diagnosis.

Seven patients (21%) died during the study period. Four patients died 2–6 years after diagnosis (11, 14, 18 and 36 months after the end of steroid treatment) with no apparent activity of the COP. The cause of death was myocardial infarction (a 68-year-old man), hematological disease (a 64-year-old woman) and stroke (2 men, 62 and 80 years of age, respectively). Two patients died during steroid treatment, after suffering multiple relapses, 2 and 11 years after diagnosis (a 78-year-old man with rupture of an abdominal aneurysm and a 76-year-old man with disseminated tuberculosis). The remaining patient, a 61-year-old man, died of respiratory failure and sepsis due to *Acinetobacter baumannii* 1 year after diagnosis, while on treatment with prednisone (50 mg/day) and cyclophosphamide.

Adverse effects to steroid therapy were reported in 17 of 32 (53%) patients, including weight gain (12 patients), osteoporosis (5 patients), hypertension (4 patients), systemic infection (3 patients, in 1 of them being fatal), diabetes (2 patients), hyperlipidemia (2 patients), and cataracts, fatty liver, cerebral pseudotumor, myopathy and pitting edema in 1 patient each. One or more complications were reported in 7 of 14 (50%) patients of the NR group and 10 of 18 (56%) patients of the RG group (non-significant).

Discussion

The main finding of the present study was the fact that most patients with COP have a high tendency to relapses. The duration of treatment may affect outcome. Relapses used to respond to steroid therapy without apparent functional or radiographic sequels. These characteristics may help to differentiate COP from other alveolar fibroblastic processes.

Incidence of OP

This study, with case recruitment based on histopathology files, represents the experience of OP in a unique center during the last 19 years. Two events marked somehow the frequency of OP in our setting: the spontaneous occurrence of an outbreak of dye-related OP in textile workers [15] and a study designed to find out the frequency and characteristics of OP adjacent to lung cancer [14]. Although this latter study could have affected the actual frequency rates of the different types of OP, the results, once adjacent forms are excluded, show that secondary OP is more frequent than the idiopathic form.

Diagnostic Criteria

To consider OP as cryptogenic, first any cause or associated disorder must be ruled out [24]. To rule out infection as the cause of OP poses frequently a difficult diagnostic challenge. Polymorphonuclear aggregates or necrosis may disappear as a consequence of the reparative proliferation [25]. Moreover, infectious OP is frequently related to atypical agents, but routine serology, recommended by Davison et al. [1], is not always performed. In fact, 40% of our patients were not serologically tested, and this may have led to an overdiagnosis of idiopathic forms. To avoid this and because most patients with OP undergo empirical antibiotic therapy, it seems convenient to exclude as idiopathic those cases that resolve 'spontaneously' or without steroid therapy. Some series, however, have considered OP as idiopathic in these patients [26]. On the other hand, in the present study, patients who presented criteria of infectious OP remained in this category irrespective of the need for additional steroid therapy for resolution. In community-acquired pneumonia, radiographic persistence or progression can occur even with appropriate antimicrobial therapy [27]. In these cases, the intraluminal fibroblastic response elicited by the infection is responsible for disease progression, and addition of steroid therapy for its resolution is mandatory [18].

Transbronchial lung biopsy has been considered inadequate for studying bronchioles, and for this reason open

lung biopsy has been recommended for the definitive diagnosis of COP [2]. However, a previous study using lung resection samples for diagnosis demonstrated [14] that the preferential sites of granulation tissue deposition seem to be alveolar ducts and alveoli. In this report, alveolar fibroblastic plugs were found in all 33 patients with OP adjacent to lung cancer, while only in 8 of them proliferative intrabronchiolar lesions could be demonstrated. Contrarily to bronchioles, alveoli are easily accessible by transbronchial biopsy, and the specimens obtained by this technique are frequently representative. On the other hand, since the small size of lung specimens may miss adjacent associated disorders, series as the present one and that of Davison et al. [1] with a high number of patients diagnosed by transbronchial biopsy, may convey a lower diagnostic specificity. Nevertheless, the long follow-up time of the present study helps to avoid the inclusion of false idiopathic forms. In fact, most investigators accept that transbronchial biopsy can confirm the diagnosis, provided the salient histological features are present and alternative causes are reliably excluded [24, 28].

The role of BAL in the diagnosis of COP is controversial [22, 29]. It has been proposed as an alternative diagnostic approach to open lung biopsy [29]. However, almost all reported cases were confirmed pathologically. In the present study, the BAL was abnormal in the 12 patients in whom this procedure was performed; however, the findings were not specific.

Chest X-Ray

In contrast to other pulmonary interstitial disorders, the predominant alveolar character of the infiltrates that appear in COP makes easy its radiographic identification. In the present series, neither chest CT nor high-resolution CT added valuable information to that provided by standard radiography. The absence of radiographic abnormalities makes highly improbable any presence of COP. In fact, Epler et al. [2], in their original description of BOOP, found and excluded a heterogeneous group of 10 patients whose biopsy specimens revealed bronchiolitis obliterans without patchy pneumonia.

Relapses

The present study and that of Lazor et al. [28], with similar stringent inclusion criteria, show that more than half of the patients with COP present relapses in spite of an apparently correct treatment. In both series, the relapse rate was 58%, being higher than in other previous large series, where the relapse rate varied from 9 [21, 30] to 39% [31].

Although a recruitment bias resulting in overrepresentation of relapsing cases cannot be ruled out [28], relapse seems to be a characteristic of genuine COP. The association of relapsing forms to a multifocal radiographic pattern in the present study reinforces that hypothesis. Forms of OP with a unique infiltrate (focal OP) may represent a different entity [8], as the frequent cure after surgical resection seems to indicate. On the other hand, a diffuse interstitial pattern is frequently seen in secondary forms [32].

It is unclear and somehow perplexing why non-relapsing forms present higher serum levels of hepatic enzymes, although usually within the normal range. Just the opposite was found in the work of Lazor et al. [28], where patients with relapses presented mild cholestasis. Similarly, higher levels of liver enzymes, suggesting cholestasis, have previously been recognized in patients with an infrequent form of COP precisely characterized for its seasonal recurrences [17].

The delay between first symptoms and treatment onset has been signalled as a predictor of relapse [28]. In that study, patients undergoing steroid treatment with a delay of over 16 weeks had a significantly higher probability of relapse. Based on this, a possible explanation for the high relapse rate found in their series was the prolonged duration of illness prior to diagnosis. In the present study, no relationship between a delay in treatment onset and relapses, neither using the average nor a cutoff of 16 weeks, could be found.

Outcome

It has been referred that 65–80% of patients with BOOP recover totally, either spontaneously or with corticosteroid therapy [33–35]. On the other hand, BOOP mortality has been estimated at 3–13% [20]. In the present series, 5 (15%) patients had not recovered while still on steroid treatment at the end of the follow-up. The inclusion of some secondary forms, not unusual as previously signalled, could explain the discrepancy among series. In the series of Lohr et al. [12], comparing idiopathic with secondary forms, 5-year survival was higher in COP (73%) than in secondary OP (44%), and respiratory-related deaths were more frequent in patients with secondary OP. In fact, most series with rapidly progressing BOOP included a substantial number (10–30%) of patients with secondary forms, e.g. those associated to collagen vascular diseases [32], extrinsic allergic alveolitis [32] and toxic exposure to gas or fume [15]. In COP patients, death directly related to the interstitial disorder is infrequent. In the series by Lazor et al. [28], respiratory

failure requiring mechanical ventilation with a favorable outcome occurred in only 1 of 48 patients. In the present series, only 1 patient (3%) showed progression of the interstitial disorder in spite of treatment and died of respiratory failure.

Treatment

Although steroids are considered the cornerstone of therapy for COP patients, due to the rarity of these idiopathic forms, studies assessing optimal dosing or duration of therapy are lacking. Relatively high-dose steroid therapy followed by long-term tapering over a period of a year has been recommended [36]. Nevertheless, the results of recent studies cast some doubts on the convenience of following that recommendation. Since apparent functional or radiographic deterioration is often absent in relapsing patients, as the present study confirms, prolonged therapy to suppress relapses appears unnecessary. That finding together with the frequent presence of adverse effects of corticoids [21, 28] favor the recent proposition of using lower doses and shorter treatment duration [28]. However, the higher probability of relapses found in this study in patients in whom the initial steroid therapy was maintained for a shorter period of time, probably as a consequence of a shorter time to chest X-ray normalization, may caution against this last recommendation.

In summary, the results of the present series come to reinforce the idea that COP is almost always a steroid-responsive inflammatory interstitial process, which resolves without functional or radiographic sequels. Relapses are a frequent and typical characteristic of COP that usually resolve with ulterior treatment. Multifocal opacities in chest X-rays and a shorter duration of the initial steroid dose may increase the risk of relapses.

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