Organizing pneumonia revisited: insights and uncertainties from a series of 67 patients

A.L. Vieira, A. Vale, N. Melo, P. Caetano Mota, J.M. Jesus, R. Cunha, S. Guimarães, C. Souto Moura, A. Morais

1 Pulmonology Department, Hospital de Braga, Braga, Portugal; 2 Pulmonology Department, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal; 3 Pulmonology Department and Diffuse Lung Diseases Study Group, Centro Hospitalar de São João, Porto, Portugal; 4 Faculdade de Medicina do Porto, Universidade do Porto, Porto, Portugal; 5 Radiology Department, Centro Hospitalar de São João, Porto, Portugal; 6 Pathology Department, Centro Hospitalar de São João, Porto, Portugal

Abstract. Background: Organizing pneumonia (OP) is classified as an acute/subacute pneumonia according to the American Thoracic Society/European Respiratory Society statement (2013 update). Although its clinical presentation, radiologic and histologic features are well established, data on the relevance of potential causes, corticosteroid doses and length, or management of relapses are based on heterogeneous series of patients. Objectives: The aims of this study were to describe clinical presentation, diagnosis and treatment of OP, explore potential causes, discuss strategies for managing relapses, and analyze prognostic factors. We also discuss our findings in relation to relevant data in the literature. Methods: We performed a cross-sectional study of all patients diagnosed with OP at a tertiary referral center in northern Portugal between 2008 and 2015. Results: Sixty-seven patients were diagnosed with OP over the 7-year study period. Dyspnea and cough were the most common presenting symptoms and approximately 30% of patients were hospitalized at the time of diagnosis. Approximately half of the patients were receiving drugs described as potential causes of OP. Microorganisms were isolated in approximately one-third of patients. Other potential causes identified were hematologic disorders, neoplasms, connective tissue diseases, myelodysplastic syndromes, immunodeficiencies, radiotherapy, and bird exposure. Cryptogenic OP was diagnosed in just 16 patients (23.8%). Corticosteroids were the most common treatment and 11 patients (16.4%) experienced relapse. Conclusions: The findings for this series of patients confirm the extreme variability of the contexts in which OP can occur and suggest that rather than a distinct, homogeneous clinicopathologic entity, OP is a non-specific reaction whose outcomes are dependent on the cause. (Sarcoidosis Vasculit Is and Diffuse Lung Dis 2018; 35: 129-138)

Key words: organizing pneumonia, acute interstitial pneumonia, subacute interstitial pneumonia, corticoids, macrolides

Abbreviations

OP: organizing pneumonia
ATS/ERS: American Thoracic Society/European Respiratory Society
ESR: erythrocyte sedimentation rate
CRP: C-reactive protein
HRCT: high-resolution computed tomography
BAL: bronchoalveolar lavage
CTD: connective tissue disease
CVID: common variable immune deficiency
COP: cryptogenic organizing pneumonia

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Correspondence: Ana Luísa Vieira
Hospital de Braga, Rua das Sete Fontes, 4710-243 Braga
E-mail: analuisapvieira@gmail.com
Introduction

Organizing pneumonia (OP) is an interstitial pneumonia that was included in the subgroup of acute/subacute pneumonias in the 2013 American Thoracic Society/European Respiratory Society (ATS/ERS) classification of the idiopathic interstitial pneumonias (1). First described as a clinicopathologic entity by Davison et al. in 1983 (2), OP is associated with a histologic pattern characterized by intra-alveolar buds of granulation tissue consisting of fibroblasts and myofibroblasts intermixed with loose connective matrix, composed mainly of collagen (1, 3). There are two forms of OP: cryptogenic OP (COP), which has no known cause, and secondary OP, which has a known cause (3-5). Although the true incidence and prevalence of OP are unknown, a study from Iceland estimated an annual incidence of 1.97 cases per 100,000 population for OP in general and 1.10 and 0.87 cases per 100,000 population for COP and secondary OP, respectively (6). COP typically appears in patients with a mean age of 50 to 60 years and it rarely affects children (3).

Although the basic concepts of OP are well established, many questions remain unanswered due to the heterogeneity of the series described to date and the use of different approaches to investigate the role and relevance of potential causes (7-9). In addition, because OP is an uncommon condition, there is no consensus on optimal corticosteroid doses or treatment duration, or on strategies for managing relapses (3-5, 10). The main objective of this study was to provide an overview of OP in a series of patients from a tertiary referral hospital and to discuss these findings in the context of relevant data reported to date.

Methods

Study design

We performed a cross-sectional study of all patients diagnosed with OP between 2008 and 2015 at Centro Hospitalar São João, a tertiary university referral hospital serving patients mostly from the Oporto district and the north of Portugal. We analyzed clinical presentation, functional and radiologic features, potential causes, diagnostic methods, treatments, and outcomes.

Diagnosis and treatment

The patients included had all been diagnosed with OP according to the 2002 ATS/ERS International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias (11) and subsequently the updated 2013 Official ATS/ERS Statement on the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias (1). Briefly, they had clinical features and radiologic changes compatible with OP, in addition to a high BAL lymphocyte count (>40%) and/or typical histologic features of OP. Potential causes investigated included infections, drugs, radiotherapy, neoplastic disorders, autoimmune diseases, hematologic disorders, and immunodeficiencies. COP was diagnosed only after meticulous exclusion of all known causes. Patients diagnosed with COP were monitored during treatment and for at least two years after remission. In the event of relapse, they were re-evaluated for an alternative diagnosis.

The standard treatment following diagnosis was a 6- to 12-month course of corticosteroids according to protocol (40 mg/day for 3 months followed by 30 mg/day for six weeks, 20 mg/day for six weeks, 10 mg/day for three months, and 5 mg/day for three months). Doses were tapered more rapidly and over a shorter period (maximum three months) in patients with secondary OP who progressed favorably after withdrawal of a causative agent. In cases of corticosteroid intolerance, contraindication, or failure, azithromycin (500 mg three times a week) was prescribed for two years. Patients who experienced remission were followed for two years and discharged in the absence of clinical or radiologic evidence of relapse. Relapse was defined as the reappearance of characteristic infiltrates on chest images together with compatible clinical features after complete remission. Histopathologic confirmation of OP was not required for the diagnosis of relapse in the presence of typical signs. Patients who relapsed were prescribed a repeat course of corticosteroids or second-line therapy with azithromycin.

The study was approved by the institutional review board at our institution.

Statistical analysis

The following variables were analyzed: sex, age, smoking status, presenting symptoms, time from onset of symptoms to diagnosis, concomitant diseases, drug
prescription, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood cell count, bacteriological studies, including sputum and bronchial aspirates, chest X-ray findings, chest high-resolution computed tomography (HRCT) findings, lung function parameters, total and differential cell counts in bronchoalveolar lavage (BAL) fluid, OP classification, treatments, and outcome. All variables are expressed as absolute numbers and/or as relative frequencies with means (SD). Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0.

Results

Main patient characteristics

Sixty-seven patients were diagnosed with OP over the study period of seven years (2008-2015). Their mean age was 61.9 (12.2) years (range, 27-88) and they were mostly male (n=43, 64.1%) and non-smokers (n=40, 59.7%).

At presentation the majority of patients had dyspnea (n=38, 56.7%), cough (n=37, 55.2%), and/or constitutional symptoms (n=33, 49.2%). Fourteen patients (20.8%) had flu-like symptoms and 45 (67.1%) were initially suspected to have an infection. At the time of diagnosis, 28.4% of patients were hospitalized with suspected pneumonia in relation to risk factors such as older age, comorbidities, and/or respiratory insufficiency. Of these 6% had been admitted to the intensive care unit (ICU). The most relevant laboratory findings showed slight anemia (hemoglobin, 11.3 [2.6] g/dL), high leukocyte count (10.5 [7.2] x 10^9 /L), and elevated ESR (59.3 [40.9] mm/h) and CRP (113.3 [95.2] mg/L).

Chest x-rays showed predominantly multifocal and bilateral infiltrates (n=32, 47.7%), and migratory infiltrates were observed in sequential images during the diagnostic work-up in 25.5% of patients. HRCT revealed bilateral alterations in over half the patients (n=39, 58.2%). These alterations predominantly consisted of consolidations (n=53, 79.1%) with a mainly bronchocentric distribution (n=51, 76.1%). Ground-glass opacities were observed in 26 cases (38.8%). The atoll sign, which is one of the most characteristic radiologic signs of OP, was present in 12 patients (17.9%). Four patients (5.9%) had a solitary focal opacity corresponding to a solitary pulmonary nodule. Although fibrosis was observed in four patients (5.9%), it was non-progressive in all cases.

Diagnosis

The median time from onset of first symptoms to diagnosis was 90 days (range, 30-180 days). Thirty-one patients (46.2%) underwent bronchoscopy with BAL. The majority (n=15, 48.3%) had a high, predominantly CD8^+ lymphocyte count (mean 38.1 [22.4%]), although six patients (19.3%) had normal total and differential cell counts. Lung biopsy was performed in 56 patients (83.5%). The technique used in the vast majority of cases (n=54) was CT-guided transthoracic lung biopsy (Figure 1). Histologic features of OP were observed in 51 cases (94.4%).

Additionally, investigation of potential causes led to the isolation of pathogens (in sputum, bronchial aspirate, and/or BAL fluid) in 23 patients (34.3%). Almost half of the patients (n=33, 49.2%) were under pharmacological treatment with drugs previously linked to OP (21). In eight patients (11.9%), OP was associated with cancer (leukemia in five patients, lymphoma in two, and bladder cancer in one). In one patient with breast cancer, OP was considered to be secondary to thoracic radiotherapy. Five patients (7.4%) had connective tissue disease (CTD)-related OP (rheumatoid arthritis in three cases and systemic lupus erythematosus in two). Two patients (2.9%) had myelodysplastic syndrome and three (4.4%) had common variable immune deficiency (CVID). Bird exposure was identified as a potential cause in one patient, who was a pigeon breeder (22, 23). Eight patients (11.9%) had multiple potential causes. No causes were identified in 16 patients (23.8%).

Lung volumes before treatment were available for just 44 patients; 10 patients had a restrictive pattern, eight had an obstructive pattern, and two had a mixed pattern. The volumes were normal in the remaining 24 patients (54.5%). Carbon monoxide diffusion capacity values before treatment were available for 37 patients. Twenty-three (62.1%) had values under 70%, although the median value was 69.5% (range, 53%-82%). The results for all the study variables are shown in Tables 1 and 2.

Treatment and outcome

Corticosteroids were the most common treatment (n=53, 79.1%). One patient with rheumatoid
Fig. 1. a) CT-guided transthoracic lung biopsy of an OP consolidation; b) H&E, x100 - OP: lung parenchyma with edema and polymorphic inflammatory infiltrate of the alveolar walls; micropolypoid buds of granulation tissue within the alveolar spaces. Alveoli lined with reactive type II cells.

Table 1. Frequency of study variables

| Variables               | Frequency |
|-------------------------|-----------|
| Sex                     |           |
| Male                    | 43        |
| Female                  | 24        |
| Smoking status          |           |
| Smoker                  | 10        |
| Ex-smoker               | 15        |
| Non-smoker              | 42        |
| Symptoms                |           |
| Dyspnea                 | 38        |
| Cough                   | 37        |
| Constitutional symptoms | 33        |
| Expectoration           | 23        |
| Fever                   | 15        |
| Thoracalgia             | 13        |
| HRCT findings           |           |
| Pattern                 |           |
| Consolidation           | 53        |
| Multifocal opacities    | 49        |
| Solitary focal opacity  | 4         |
| Reticulonodular         | 13        |
| Location                |           |
| Bilateral               | 39        |
| Unilateral              | 27        |
| Distribution            |           |
| Bronchocentric          | 50        |
| Subpleural              | 12        |
| Subpleural and bronchocentric | 4  |
| Ground-glass opacities  | 27        |
| Atoll sign              | 12        |
| Air bronchogram         | 5         |
| Fibrosis                | 4         |
| Pleural effusion        | 3         |
| Band                    | 1         |
| BAL findings (n=31)     |           |
| Normal                  | 6         |
| High lymphocyte count   | 15        |
| CD4+ predominance       | 3         |
| CD8+ predominance       | 7         |
| Neutrophilia            | 8         |
| Eosinophilia            | 8         |
| Hemorrhage              | 1         |
| Lung function tests (n=44) |         |
| Obstructive pattern     | 8         |
| Mixed pattern           | 2         |
| Restrictive pattern     | 10        |
| Normal                  | 24        |
| Lung biopsy (n=56)      |           |
| CT-guided transthoracic lung biopsy | 54  |
| Surgical lung biopsy    | 2         |
arthritis was treated with methotrexate and leflunomide. Four of the 16 patients diagnosed with secondary OP were not prescribed corticosteroids. Two of them, both with CVID, were treated with immunoglobulin replacement therapy (in addition to azithromycin in one case), one was treated with antituberculosis agents, and the other was treated with antifungal agents (for pulmonary aspergillosis). All 49 cases of secondary OP were treated according to the underlying cause. Response to treatment was favorable in 96.2% of cases (n=51). Four patients developed intolerance to corticosteroids and were switched to azithromycin respectively. Two patients (one with COP and one with lymphoma-related OP) showed poor response to corticosteroids and were respectively prescribed azithromycin and azathioprine respectively. Four patients had mild disease and three of them were only monitored as they had significant comorbidities. Two patients with advanced cancer were prescribed palliative care only. Finally, two pa-

**Table 2. Causes of secondary OP (n=51)**

| Drug induced (n=33) | Statins | Beta-blocker | Amiodarone | Methotrexate | Sertraline | Metformin | R-CHOP (rituximab/cyclophosphamide/doxorubicin) | ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) | Cytarabine | Bleomycin | Allopurinol | Omeprazole | Everolimus/tacrolimus/bortezomib/thalidomide | Sulfasalazine | Trimethoprim sulfamethoxazole |
|---------------------|---------|--------------|-------------|--------------|------------|-----------|-----------------------------------------------|-----------------------------------------------|------------|-----------|-------------|-----------|----------------------------------|--------------|-----------------------------|
|                     |         |              |             |              |            |           |                                               |                                               |            |           |             |           |                                   |              |                             |
| Infection (n=23)    | Staphylococcus aureus | 6 | Pseudomonas spp | 4 | Streptococcus pneumoniae | 3 | Candida albicans | 3 | Enterobacter spp | 2 | Enterococcus spp | 2 | Escherichia coli | 2 | Pneumocystis jiroveci | 2 | Aspergillus fumigatus | 2 | Haemophilus influenza | 1 | Stenotrophomonas maltophilia | 1 | Acinetobacter baumannii | 1 | Mycobacterium tuberculosis | 1 | Mycobacterium avium complex | 1 | Burwell burgdorfieri | 1 | Respiratory syncytial virus | 1 | Epstein-Barr virus | 1 | Hematologic disorders (n=7) | Leukemia | 5 | Lymphoma | 2 | Connective tissue disease (n=5) | Rheumatoid arthritis | 3 | Systemic lupus erythematosus | 2 | Immunodeficiency | 3 | Myelodysplastic syndrome | 2 | Bird exposure | 1 | Radiotherapy exposure | 1 | |

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patients were lost to follow-up and one had missing information.

Relapse was observed in 11 patients (16.4%): three with COP, six with drug-related OP, one with CTD, and one with CVID. The patient with CVID was treated with azithromycin as first-line therapy and all other patients had been treated and responded favorably to corticosteroids, but four of them relapsed during treatment (prednisolone or equivalent <10 mg/day). Azithromycin was the most common second-line therapy (n=5), followed by immunosuppressant azathioprine (n=2). One patient with systemic erythematous lupus was treated with azithromycin plus azathioprine and a patient with drug-related OP started a second course of prednisone in association with azithromycin. Two asymptomatic patients with small nodules on the HRCT scan were monitored using a watch-and-wait approach. One patient prescribed azithromycin had macrolide intolerance (azithromycin and clarithromycin) and was prescribed intravenous cyclophosphamide pulse therapy. Three patients, one with COP and two with drug-induced OP (two treated with azithromycin and one with cyclophosphamide), experienced further relapses and were diagnosed with chronic OP and administered a long course of azathioprine. The disease regressed in one case and stabilized in the other two. There were no OP-related deaths during the treatment period.

**Associations according to type of OP and predictors of relapse**

No differences were found between patients with COP and secondary OP in terms of presenting signs, type or severity of symptoms, laboratory or lung function test results, radiologic or pathologic findings, or outcomes. Differences between patients who relapsed and those who experienced remission were also non-significant.

**Discussion**

In this series of 67 patients diagnosed with OP only 16 patients (23.8%) had COP and a wide range of potential causes including infections, drugs, CTD, hematologic diseases, and CVID were identified. This diversity of potential causes calls into question the definition of OP as a clinical entity and suggests instead that it might be a non-specific pathologic process that occurs in a multitude of contexts. Outcomes were generally favorable, with good response to both corticosteroids and azithromycin and a low relapse rate.

The clinical features of OP were consistent with those reported in other series (3, 12-15). Mean age of onset was in the range of 50-60 years and non-smokers were more common. There was a slight male predominance, although no particular predilection for sex has been reported in the literature. The mean time from onset of symptoms to diagnosis (six months; median, three months) is longer than that reported elsewhere (<3 months) (12). This is probably attributable to the significant proportion of patients with mild symptoms who were initially treated for a suspected infection. OP is a rare condition and may be unfamiliar in some primary care settings. Although our findings confirm that subacute OP, with flu-like symptoms, is the most common presenting form of OP, 28.4% of the patients in our series had an acute presentation requiring hospitalization, and 6% of these were in the ICU at the time of diagnosis. Although acute presentations have been described in other series (1, 3, 4), prevalence rates are considerably lower than in our case (14-18). This may be because our study was performed in a tertiary university hospital that provides emergency care for the area and has 60 ICU beds.

The vast majority of patients in our series had typical radiologic signs of diffuse opacities with a bronchocentric rather than the more common subpleural pattern in most cases. This predominance of the bronchocentric pattern can probably be explained by the high proportion of patients with secondary OP (5). Only four patients had a solitary focal opacity and no infiltrative variants were observed.

Biopsy, and CT-guided transthoracic lung biopsy in particular, was the main diagnostic tool used. CT-guided transthoracic lung biopsy is a very simple procedure for obtaining direct samples from lung opacities, and it is also highly effective, with a diagnostic yield of 94.4% in this series. Although histology is a key diagnostic tool, BAL should always be considered as it enables the detection of high lymphocyte counts, microorganisms, and malignant cells.

The proportion of patients diagnosed with COP in our series is significantly lower than that reported in the few series described in the literature (3, 4, 7-9,
Thirty-two patients in our series were taking drugs identified as potential causes of OP. Pneumotox, which is a database of drug-induced respiratory diseases, contains 99 drugs that have been linked to OP (19). Lipid-lowering agents, such as statins (the main drug-related cause in our series), antiarrhythmic agents, such as amiodarone, and antidepressants, such as selective serotonin reuptake inhibitors, are among the main drug classes involved. Identification of statins as a cause of OP can complicate clinical decision-making in certain patients with dyslipidemia due to the lack of alternative drugs with similar effectiveness. The high number and range of microorganisms reported as potential causes of OP suggests that OP may occur in all types of lung infections. OP should therefore always be contemplated in the differential diagnosis when a patient does not respond favorably to treatment for an infection. Our findings confirm the important role of microorganisms in OP, as we identified 17 different agents, including bacteria, fungi, and viruses, in 23 patients (34.3%). Some of the microorganisms detected are typically found in association with more serious events characterized by significant respiratory insufficiency and prolonged hospitalization. Examples are Pseudomonas spp, Stenotrophomonas maltophilia, Acinetobacter baumannii, Pneumocystis jiroveci, and some strains of Streptococcus pneumoniae and Staphylococcus aureus. The large number of infected patients could help to explain the relatively high proportion of patients who were hospitalized at the time of OP diagnosis. We also identified a case of pulmonary tuberculosis, which has been linked to OP on rare occasions. In the few reports that exist (including ours), a favorable outcome was achieved only with antituberculosis agents (17-18), suggesting the need for a rather different therapeutic approach to that usually considered in OP. Another less common association described in the literature is that of OP and Aspergillus species (20-21), although in the cases reported, disease control was achieved with a combination of corticosteroids and antifungal agents.

Concomitant disorders, such as CTD, are also important causes of OP. While the most common interstitial pneumonia in patients with CTD is nonspecific interstitial pneumonia, patients can develop all types of interstitial pneumonia, including OP (22, 23). Identification of the cause of OP in such cases can be truly challenging because of the drugs used to treat CTD and the risk of opportunistic infections. It seems to be clear, however, that CTD-related OP is associated with higher relapse rates and longer treatment times than other forms of OP, probably because of the chronic nature of the underlying condition (4, 24, 25). Outcomes in the five patients with CTD in our series were similar to those in the group overall, but the small sample size prevents us from drawing any conclusions in this respect. In addition, these patients were all receiving immunosuppressive therapy, which is a confounding factor.

Different types of cancer are associated with OP (3-5, 10). In our series we found a significant predominance of hematologic disorders. Five patients had leukemia, two had lymphoma, and just one had a solid neoplasm (bladder cancer). As in CTD, opportunistic infections and confounding factors, such as chemotherapy, can make it difficult to identify the cause of OP. In addition, the outcome in such cases is linked to the severity of the underlying cancer, as complicated infections and disease progression can prevent favorable responses to treatment. In our series, all the patients with cancer except one receiving palliative care responded favorably to OP treatment. At the time of diagnosis, they were all under treatment for their cancer and response was also favorable in this case. Although thoracic radiotherapy for lung cancer or lymphoma can cause OP, most of the cases described to date, like ours, have been in patients with breast cancer (3, 10, 26). The reasons for this particularity are unclear, but they could be related to, among other factors, tangential field irradiation or hormonal factors, as suggested by a study in which antiestrogenic therapy was associated with an increased risk of OP (27).

CVID is another condition increasingly described in association with OP (28, 29). Three patients in our series had CVID. They all had mild forms of the disease and were receiving immunoglobulin replacement therapy. One of the patients initially prescribed corticosteroids was switched to azithromycin after four weeks because of intolerance.
and another one was treated with azithromycin as first-line therapy. The first patient experienced remission, but the second one relapsed. He remained asymptomatic, however, after a second course of azithromycin and was monitored without additional treatment as he experienced no further functional impairment. The third patient had small chronic migratory opacities on x-rays, but was also recommended for observation due to the absence of symptoms, functional deterioration, and radiologic evidence of disease progression.

There were no cases of inflammatory bowel disease in our series. This is surprising as the study was conducted in a referral hospital and inflammatory bowel disease is a common cause of OP. Bird exposure was identified as a potential cause in one patient. This cause is relatively unknown given the few cases reported (13, 16). Clinicians, however, need to consider exposure not only to living birds but also to goose and duck down in pillows or duvets (26). Given the multiplicity of potential causes, it is crucial to question all diagnoses of COP and rigorously investigate all potential causes as they can have a significant impact on patient outcome. Clinicians must also be aware of rare potential causes, such as exposure to fumes and toxic substances (e.g., aerosolized textile dye, mustard gas, house fire smoke, food-spice flavoring, heated paraffin oil) (3, 26). In addition, there are almost certainly other causes that have not yet been identified.

The use of corticosteroids in OP has not been investigated in clinical trials, and therefore recommendations on drugs, doses, and treatment duration are based only on experience and data from clinical series (3, 5, 10). There is, however, ample evidence that corticosteroids are effective in inducing disease regression (3-5, 10, 26). Although corticosteroids are largely considered to be the treatment of choice for OP, dosing and treatment duration are more controversial. Wells et al. (5) recommend high doses of intravenous methylprednisolone administered over three days (0.75-1 g), followed by 40 mg/day of prednisolone for 10 to 14 days, 10 mg/day for the next one to two months, and 20 mg on alternate days for a year or longer if there is evidence of limited interstitial fibrosis. Epler (38) also proposed starting with high doses of prednisone (1 mg/kg/day) for one to three months, followed by 40 mg/day for three months and 10 mg/day for a year, although he also considered that an initial dose of 40 mg could be administered for less severe disease and that six months of treatment may be sufficient for moderate disease (26). King and Mortenson (39) recommend starting with high doses of prednisone (1-1.5 mg/kg/day for 4-8 weeks) and then tapering to 0.5 to 1 mg/kg/day for four to six weeks. They additionally suggested gradually tapering the dose to zero if the patient’s condition remained stable or improved after three to six months of treatment. Cordier’s group proposed a treatment protocol consisting of lower doses and shorter treatment times, starting with 0.75 mg/kg/day of prednisone for four weeks, followed by 0.5 mg/kg/day for six weeks, 20 mg/day for three months, and then 5 mg/day for six weeks (3, 4, 10).

Our approach, described in the methods section, falls somewhere in between and consists of lower doses administered over the period of a year. While not supported by evidence, our approach is based on the theory that corticosteroid treatment over one year might be associated with a lower risk of relapse (10). Patient preferences should also be taken into account when weighing up the balance between the risk of more relapses and that of fewer adverse effects, because although relapses are usually responsive to corticosteroids, they imply active disease and this has both a clinical and physiological impact on patients. Patients with acute OP, i.e., hospitalized patients, are generally prescribed higher doses of corticosteroids on diagnosis. In patients with secondary OP who respond favorably to the withdrawal of a causative agent, doses are tapered more rapidly and treatment lasts for just six months. Data on relapse rates during corticosteroid tapering or withdrawal are highly variable, with figures ranging from 13% to 58%. This variability could be related to differences in the make-up of the series, as relapse is more common in patients with secondary OP. It could also, of course, be influenced by differences in treatment regimens. Numerous factors have been associated with a higher risk of relapse, including delayed treatment, mild cholestasis (37), severe hypoxemia (40), greater disease extension, whether with radiologic lung opacities or histologic multifocal fibrin deposits (41), and presence of gastroesophageal reflux (42). The relapse rate of 16.4% observed in our series is low, particularly considering the predominance of secondary OP. We found no associations between relapse and clinical or radiologic findings, but this
could be due to a lack of statistical power. Moreover, it could be speculated that because outcomes in secondary OP are dependent on controlling the underlying disorder or eliminating the cause, studies of predictors should possibly only include cases of COP. Choice of treatment in patients who relapse is less clear. Although corticosteroids administered at lower doses over shorter periods are recommended and are usually associated with a favorable response, there is increasing evidence that macrolides are effective and well tolerated (43-47). They are also, of course, an option in rare cases of corticosteroid intolerance. The anti-inflammatory mechanism of macrolides includes inhibition of cytokine production in the alveolar macrophages, decreased release of superoxide and elastase from stimulated neutrophils, impaired phagocytic oxidative neutrophil bursts, decreased neutrophil chemotaxis and survival, and importantly for OP, increased apoptosis of lymphocytes and increased apoptosis of neutrophils, histiocytes and eosinophils (48-51). In our cohort, 10 patients were prescribed azithromycin: five following relapse and five following OP diagnosis due to intolerance of failure to respond to corticosteroids. The effectiveness of macrolides as a first-line treatment was confirmed, as just one patient relapsed. Two of the patients who received azithromycin following relapse experienced further relapses.

Conclusions

Our findings confirm the enormous variability of contexts in which OP can occur, suggesting that it is more a non-specific reaction than a distinct clinicopathologic entity. There was also considerable variability in terms of outcome, which appeared to be dependent on the course of the underlying disease. The conclusion would appear to be that all potential causes of OP must be thoroughly investigated. Despite some controversy about doses and treatment duration, our findings confirm that corticosteroids are highly effective and provide further support for the potential role of macrolides as an alternative.

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