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Organizing pneumonia: Manifestation Peculiarities, Causes, and Outcomes

Research Article

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Abstract: Introduction: Organizing pneumonia (OP) is a rare disorder which may be associated with various clinical contexts and radiological patterns. Objectives: To evaluate prospective peculiarities of the manifestation of OP, which may improve the of characterization of the disorder. Material and Methods: Forty consecutive patients with a biopsy proven OP were investigated. Clinical symptoms, radiographic signs, and laboratory indices (complete blood cell counts, CRP level, BAL fluid examination) were examined. All patients underwent investigation for possible underlying pathology and associations. Results: 62.5% of patients had mild-to-moderate respiratory symptoms, 17.5% had severe respiratory symptoms, while the remaining 20% were asymptomatic (an incidental finding on chest radiographs). Severity of the disease correlated with CRP level, but did not correlate with blood leukocytes. Multiple bilateral infiltrates were detected in 35%, a single infiltrate in 40%, a solitary mass in 12.5%, multiple small nodules in 10%, and diffuse ground glass appearance in 2.5% of all cases. Air bronchograms were present in 45%, cavitations in 12.5%, and pleurisy in 7.5% of all lesions. OP occurred in association with infections (53%), neoplastic diseases (23%), both (7%), and other disorders (7%). A cryptogenic origin of OP was in 10% of all cases. Conclusion: OP mostly manifested with mild-to-moderate respiratory symptoms and single or multiple lung infiltrates. OP varied in clinical and radiological forms. OP associated mostly with infection and/or neoplasm in our patients. Other reasons and cryptogenic origins of the disorder were rare.

Keywords: *Interstitial lung disease • Organizing pneumonia • Pneumonia*

1. Introduction

Since 1983 when organizing pneumonia (OP) was originally described by Davision et al. [1] and subsequently reported by Elper et al. in 1985 [2], there still has been several unanswered questions related to its clinical significance, treatment options, etc. [3]. OP is a histological pattern characterized by air-space-filling fibroblast plugs with the surrounding relatively normal lung [4]. OP may be idiopathic (cryptogenic), but there are several known causes of OP and several systemic disorders have organizing pneumonia as an associated

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primary pulmonary lesion [5]. OP is often found in association with non-resolving infectious pneumonia [3]. However, in clinical practice, it is not easy to distinguish between OP and non-resolving infectious pneumonia [6-8]. Moreover, OP may be related to lymphoma [9] or carcinoma [10]. OP is a relatively rare entity [11]. Since clinical manifestation is nonspecific and imaging patterns are various, diagnosis may often be delayed [12].

There are several excellent publications designed to cryptogenic OP [13-15]. However, only a few original studies [16] were intended for the evaluation of both - cryptogenic and secondary OP. There is a lack of prospective studies.

In 1997, the Clinic of Chest Diseases, Allergology, and Radiology of Vilnius University (Lithuania) launched a study of interstitial diseases. The aim of this study was to evaluate prospectively clinical symptoms, the diagnostic role of bronchoscopy, the course of the interstitial diseases, and other related issues. The aim of this particular part of the study was to evaluate peculiarities of manifestation, causes, and outcomes of OP, as this may allow an improvement in characterization of this disorder.

2. Material and Methods

It was a study conducted between 1997 and 2009 in the Centre of Pulmonology and Allergology of Vilnius University Hospital *Santariškių klinikos*. The patients were recruited to the study after they underwent bronchoscopic lung biopsy (BLB) and OP was morphologically confirmed. BLB was performed mostly due to a non-resolving lung infiltration or multiple bilateral infiltrates. The study population consisted of all the patients who were newly diagnosed OP in our Centre during the study period.

A signed Inform Consent Form, approved by the Hospital authorities, was obtained from all the participants. All the patients were investigated on complaints, clinical symptoms, blood laboratory indices (haemoglobin level, erythrocyte sedimentation rate, complete blood cell counts, CRP level, blood gases, and biochemistry), chest x-rays and computed tomography (CT) scans of the lungs, and bronchoalveolar lavage (BAL) fluid cytological and microbiological examinations.

Patients were considered asymptomatic if they had no complaints (an incidental finding on examination of chest radiographs). Clinical symptoms were considered mild-to-moderate when patients had a cough, dyspnoea due to exercise, or a fever. OP was considered severe in the case of respiratory failure or when the patient was hemodynamically unstable.

The radiological appearance of OP (according to the CT examination) was allocated according to single infiltrate, multiple infiltrates, solitary mass (solid collection of tissue > 30 mm in diameter), multiple small nodules (rounded opacity of at least soft tissue attenuation with a diameter ≤ 7 mm), and diffuse ground glass appearance.

A bronchoscopic lung biopsy was performed at the Centre of Pulmonology and Allergology of Vilnius University Hospital *Santariškių klinikos.* Bronchoscopic lung biopsy is a suitable method to recognize the histological pattern of OP [4,14,17].

The bronchoscopic lung biopsy (BLB) samples were examined at the Lithuanian National Centre of Pathology (Vilnius, Lithuania), which is accredited by the College of American Pathologists. The diagnosis of OP was based on a bioptic proof of intraluminal fibroblast plugs in distal air spaces (documented by lung biopsies in all cases) [14].

After the results of the morphological studies of the BLB samples became known, patients underwent additional investigation for possible a underlying pathology and associations as approved standard in our Centre. The standard included an examination for immunologic blood markers for rheumatologic and connective disorders, for bronchoalveolar lavage (if not performed during first bronchoscopy) with cultures for bacteria, fungi, mycobacterium tuberculosis, abdominal, and kidneys sonoscopy, and additional investigation if necessary. Bronchoalveolar lavages and bronchoscopic lung biopsies were performed in the way we had comprehensively described in previous publications [18,19].

The follow-up of most of these patients, as approved by our Centre, has lasted for at least 1 year (up to 3 years in this patient population). Other possible disorders were excluded. The follow-up investigation, which included a clinical and blood indices examination, and a chest X-ray, was dedicated to revealing possible underlying disorder and survival as well. The investigation does so several times: 1 month, 3 months, 6 months, one year, or longer if necessary after discharge.

Statistic data were processed at the Department of Mathematical Statistics of Vilnius Gediminas Technical University. Statistical data processing was performed by SPSS 15.0 Programme. For normally distributed continuous variables (*i.*e. type of radiological pattern did not correlate with the type of OP), Pearson correlation coefficients were performed. For abnormally distributed continuous variables (*i.e.* severity of clinical manifestation performed and CRP level), Spearman correlation coefficients were derived. In all tests, a *P* value of less than 0.05 has been considered to be statistically significant.

Table 1. Radiological pattern of the study patients.

Pattern	Number (percentage)
Single infiltrate	16 (40)
Multiple bilateral infiltrates	14 (35)
Solitary mass	5 (12.5)
Multiple small nodules	4 (10)
Diffuse ground glass appearance	1 (2.5)

3. Results

3.1. Study Population

The study population consisted of 40 consecutive OP patients. There were 27 males and 13 females. The average age was 56 years (range 22-79 yrs). 32 patients were non-smokers and 8 were current or ex-smokers. At the time of diagnosis, none of the patients were in need of mechanical ventilation. None of the patients were treated with steroids.

All of the patients underwent a bronchoscopic lung biopsy. An average of 9 biopsies (range 4-14 biopsies) was obtained for each patient. Most of the samples were 2-3 mm in diameter. In all of the patients, a typical histological pattern of OP was found. However, when the results of BLB became available, 2 patients underwent a surgical lung biopsy due to an abnormal OP radiological pattern. Out of the 40 patients, 20 underwent BLB and bronchoalveolar lavage (BAL) for microbiological and/or cytological studies (the choice depended on the clinical situation).

3.2. Disease Manifestation

Initial symptoms of OP were coughs (80%), fevers (63%), dyspnoea (26%), and hemoptysis (2.5%). Twenty-five (62.5%) of all 40 patients had mild-to-moderate symptoms, 7 (17.5%) had severe symptoms, and the remaining 8 patients (20%) were asymptomatic. The mean disease duration of the symptomatic patients before establishing a diagnosis was 5.5 weeks (range 1-14 weeks).

The C-reactive protein (CRP) was increased (>5 mg/L) in 82 percent of the patients (the median was 22 mg/L, range 1-244 mg/L). The blood leukocyte count was increased (>9.0 $x10^9$ /L) in 55 percent (the median 9.4 $x10^9$ L, range 2.7-60 $x10^9$ /L). The severity of the disease correlated with CRP level ($r = 0.515$, $p < 0.01$), but did not correlate with blood leukocytes, radiological manifestations, or cause/underlying disorders.

Cultures of the BAL fluid were positive in 4 cases (one with *Streptococcus pneumonia* and *Staphylococcus aureus*, respectively, and two with a combination of different bacteria). A standard cytological examination of the BAL fluid revealed three different patterns (with an increased count of lymphocytes, neutrophils, or both), but they themselves were non-diagnostic (data not shown).

Organizing pneumonia manifested with different radiological patterns, mostly with single or multiple infiltrates (Table 1). Air bronchograms were present in 18 (45%), cavitations were present in 5 (12.5%), and pleurisy in 3 (7.5%). The type of radiological pattern did not correlate with the type of OP (cryptogenic or secondary).

3.3. Causes and Associated Disorders

Organizing pneumonia occurred in association with infection in 21 cases (53%), neoplastic disease in 9 cases (23%; 6 haematological malignancies and 3 carcinoma), both in 3 cases (7%), and other disorders in 3 cases (7%; one associated with amiodarone, autoimmune hepatitis, and dermatitis each). Four of all 12 patients with neoplastic disorders had lymphoma, 3 had leukaemia, 1 had myeloma (all diagnoses were known and all the patients were treated before OP was established), 2 had lung cancers (one of them documented by an open lung biopsy), 1 had solitary metastasis in the lung of ovarian carcinoma (documented by an open lung biopsy), and 1 had kidney carcinoma (patient has been operated several years ago, but without specific treatment at the time when OP was diagnosed). In one case of the carcinoma of the lung and the case of ovarian cancer metastasis OP localized adjacent to neoplasm. In the second case of the carcinoma of the lung, cancer was revealed in segmental bronchus of the contra-lateral lung to OP when a bronchoscopy for non-resolving pneumonia was performed and biopsies from both sites were taken.

Surprisingly, no cases of collagen-vascular disorder were diagnosed, though the patients have been purposely examined. A cryptogenic origin (without any possible associations at the time of diagnosis and follow-up period) of OP was in 10% of all cases.

3.4. Courses and Outcomes

Corticosteroids were administrated to 21 (52.5%) patients, while 19 (47.5%) patients were observed without the administration of corticosteroid therapy. We hesitated to prescribe corticosteroids for all of our patients due to the high risk of reactivation of tuberculosis (the prevalence of latent and active tuberculosis in Lithuania is still high) [20]. Moreover, 1 month later, after the complete resolution of OP in the follow-up period, one patient with a certain cryptogenic OP, who was treated with corticosteroids, developed

active tuberculosis of the lung (with different localization and different radiological pattern, and positive culture). The patient was completely cured with antituberculosis drugs.

There was delay of radiological resolution in most of the cases. The average time to complete resolution after diagnosis verification was 10 weeks (range 5-18 weeks, or up to 24 weeks if an add period till diagnosis was established). One patient with leukaemia associated OP has died. However, no relapses were observed in the remaining patients.

4. Discussion

Organizing pneumonia is a rare disorder and the exact prevalence remains unknown. According to a recently published nationwide epidemiology study in Iceland, the mean annual incidence of OP (both cryptogenic and secondary) was 1.97 per 100 000 people, which is much higher compared to the findings of other researchers [11]. Several months of illness may continue before the correct diagnosis [13,22]. In one of our cases, organizing pneumonia was diagnosed after 14 weeks of the disease onset. Most of our study patients were treated for infection-like symptoms and pulmonary infiltrates with several courses of different antibiotics until they were referred to our tertiary university hospital for differential diagnostics. The clinical symptoms of the study patients were in agreement with those previously reported [10,13,16]. However, OP may be present with non-typical clinical symptoms such as rapidly progressive life-threatening syndrome [23,24] or large-quantity hemoptysis [25].

Our experience reveals that in clinical practice, OP usually may be suspected almost exclusively when pulmonary infiltrates are not resolved or improved after multiple antibiotic courses. The imaging pattern of OP is heterogeneous. Possible pulmonary lesions included unilateral or bilateral patchy consolidations in subpleural or peribronchial distribution, multiple nodules, single nodule, or mass, etc. All of them may be with or without air bronchograms, cavitations, or reverse halo sign [8,26-32]. However, in our opinion, at least half of all cases could be diagnosed much earlier if diagnosed properly. We agree with Cordier [33] that the radiographic and computed tomography findings are often so characteristic that they suggest the diagnosis, especially, in our opinion, multiple non-segmental infiltrates with air bronchogram. This pattern is very typical for chronic eosinophilic pneumonia (CEP) as well [34], but these disorders particularly differ in laboratory findings (blood and BAL fluid eosinophilia are very typical for CEP) [21].

Although no definitive conclusion may be drawn, it is likely that some of the OP cases of the patients in our series that were assigned to the post-infection form were actually cryptogenic in origin. There is no good way to discriminate them in clinical practice. Described clinical manifestations of cryptogenic OP [12] included flu-like illness with fever, cough, malaise, and progressively mild dyspnoea, which occasionally may be severe anorexia and weight loss. It is usually indistinguishable from OP due to a slowly resolving infectious pneumonia.

Results of our study do not confirm the traditional proposition that idiopathic is the most common type of OP [2]. However, OP is only considered to be cryptogenic when a definite cause or characteristic associated context is not present [12]. Post-infection OP was the majority of all the OP cases in our study, while pathogenic microorganisms have been identified to be the minority of the cases. The reason of these findings is not clear. It is likely due to the diagnostic algorithm accredited in our Centre. As was mentioned earlier, incidence of tuberculosis in Lithuania is still high. In all cases of slowly resolving pneumonia, we tried to perform BAL and/or BLB in order to rule out possible tuberculosis instead of using simple observation. If we implemented the latter, the quantum of post-infection OP would probably be fewer (due to spontaneous resolution), but we overlooked some cases of tuberculosis. However, it should be noticed that diagnostic significance of BAL fluid cytological pattern is not clear [3].

Recently published results of the retrospective study in Iceland [11] showed that secondary OP occurred as often as cryptogenic OP. Secondary OP can be related to different types of medications, including amiodarone [35,36], acebutolol [35], nitrofurantoin [37], ticlopidine [38], and anticancer drugs [39-41]. OP can occur in patients with different malignancies [10,42,43] or after radiation therapy [44]. In the light of these data, it cannot be definitely inferred that eight of our OP patients with haematological malignancies OP were related to neoplasm itself, to chemotherapy, or latent infection and/or colonization with unusual microorganisms, which is common in cases of blood disease. Moreover, various environment-related factors [45,46] or concomitant disorders, such as gastroesophageal reflux disease [47] and paraneoplastic skin disorder [48], may cause OP.

The initial steps of OP pathogenesis are probably different. A trigger of some kind (e.g. infectious agent) stimulates the inflammatory process, which leads to a final common pathway. OP can occur after a variety of different types of infectious pathogens [3,5]. OP has been described with an association to different malignancies. However, whether a true pathogenic relationship

exists between OP and malignant diseases remains to be defined [9]. The impact of T lymphocytes in the pathomechanism of OP after allogenic hematopoietic stem cell transplantation with related donors was suggested [49].

Although OP can occur in patients with connective tissue diseases [50], there was no patient with such disorder in our sample group during the study period, though two of the authors (E.D. and R.Z.) regularly consult quite a number of patients with rheumatologic disorders. The reason for the correlation between OP and connective tissue diseases is not clear. We can only speculate that our patients with connective tissue diseases were treated with corticosteroids, which prevents the development of OP.

Corticosteroids represent the current standard in the treatment of cryptogenic OP [3]. There were no relapses during the follow-up period in our patients, although several relapses occurred in patients with chronic eosinophilic pneumonia evaluated in our parallel study [21]. Relapses of OP can occur [15,51] and should prompt a search for the persisting cause of OP [3], such as malignant lymphoma [9]. However, clear recommendations for the treatment of secondary OP are lacking. In such cases, evaluating the efficacy of the treatment is difficult. Naturally, prognosis in most of cases of post-infection OP (mostly due to acute infection) is excellent and relapses are not expected. In other cases of secondary OP when the underlying disorder is cured or the external factor (e.g. medicine intake) is removed, the probability of relapses is not high.

There are certain limitations to our study. Firstly, this study was conducted at a single institution and hence, it is possible that there could be geographic variability in the presentation and causes of OP. However, our Centre is one of two referential Centres for respiratory diseases in the country and has the greatest experience in the diagnostics and management of interstitial lung diseases. It is likely that the study population represents the whole country population. Secondly, the data used for this study were collected as a part of routine clinical care. However, the study was performed prospectively with the same investigators during all the study period and the follow-up.

5. Conclusion

Organizing pneumonia has various clinical and radiological forms. OP is mostly presented with non-severe clinical symptoms, but can be asymptomatic. The severity of clinical symptoms was independent of the etiology of the disorder, but correlated with CRP level. Single or multiple pulmonary infiltrates were typical for our patients with OP. Radiological manifestation was not related to a specific OP form. Post-infection and malignant neoplasm related OP was the most common form of the disease. Cryptogenic OP in our patients was rare. Although one patient died, the overall short-term prognosis was good.

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