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Organizing pneumonia — clarithromycin treatment

Abstract

Introduction: Organizing pneumonia (OP) is a rare syndrome that has been associated with a variety of underlying factors including infections, collagen vascular diseases, toxic fumes, cancer, drugs and radiotherapy. A cryptogenic form is also observed. OP is a curable disease in the most cases. Steroids are the standard therapy, but other treatment regimens have been used as well.

Material and methods: In the period from 1999 to 2005, 9 women and 3 men (age range 44–71 years) with OP were selected for the study. There were 9 non-smokers, 2 smokers and 1 ex-smoker. Open lung biopsy was performed in 5 patients, and in 7 patients diagnosis was established on the basis of transbronchial lung biopsy.

Results: Dyspnoea (100%), cough (100%), weakness (100%), fever (83%), loss of weight (83%), sweats (33%) and chest pain (8%) were the most frequently noticed symptoms. Radiographically, all patients had bilateral consolidations with areas of ground glass attenuations. A migratory pattern of these lesions was observed in 9 (75%) patients. In all patients clarithromycin (CLA) in a dose 0.5 g b.i.d was administered. Nine (75%) patients were successfully treated. Complete clinical and radiological remission was obtained after 3 months of CLA therapy in 7 and a partial response in an additional 2 patients, in whom treatment was prolonged to 4 months. During the first month of CLA treatment 3 patients did not respond to the therapy, and prednisone was introduced. The observation period ranged from 30 to 90 months (mean 42 months). Adverse reaction to CLA and relapse did not occur.

Conclusions: OP can be treated with clarithromycin. It may be an alternative treatment, particularly for patients in good clinical status and in whom the probability of adverse events in the course of corticotherapy is high.

Key words: cryptogenic organizing pneumonia, antibiotic therapy, corticosteroid therapy, clarithromycin

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Introduction

Organizing pneumonia (OP) is a distinct clinicopathological entity resulting from a pulmonary reaction to noxious factors including infections, especially Mycoplasma pneumoniae, Chlamydia pneumoniae and viruses. It might be the consequence of exposure to toxic substances, drugs or radiotherapy. OP has been observed in autoimmunological and neoplastic disorders [1–5]. A cryptogenic (COP) form of this disease is diagnosed when the initiating factor is unknown [6, 7]. The main clinical presentation includes: flu-like onset of the disease with cough, slight fever, weakness, progressive effort dyspnoea and migratory alveolar infiltrates on chest X-rays [8–12]. In the course of OP, the inflammatory organised exudate in the alveoli and small bronchioli accumulates in the shape of characteristic polyps with the presence of a variable degree of interstitial infiltration of mononuclear cells and foamy macrophages in alveolar spaces. The structure of lung parenchyma remains unchanged [4, 5]. In general, the prognosis of the disease is good; however, a progressive form is noticed [6, 8–15]. The spontaneous regression of OP occurs in less than 5% of cases [3, 4, 8–15]. It is usually the result of drug-induced changes, which resolve spontaneously when the therapy

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with stimulating medicine is withdrawn; however, it is also observed in cryptogenic form [6, 8–16]. Steroids in doses of 0.5–1 mg/kg are the standard OP treatment, and other immunosuppressive and anti-inflammatory therapy seems to be effective as well [6, 8–15].

Macrolides present unspecific anti-inflammatory activities by diminishing the concentration of inflammatory mediators such as TNF-alpha, IL-8 and IL1- β . IL-8, produced by the endothelium and respiratory tract cells, is the essential chemotactic factor for neutrophils and plays an important role in the pathogenesis of OP [17, 18]. In addition, the anti-inflammatory activity of macrolides is connected with inhibition of elastase activity, suppression of GM-CSF (granulocyte-macrophage colony stimulating factor) and soluble adhesions molecules [19]. During macrolide treatment, inhibition of IL-6 and reduction of NO concentration is observed [18]. In the course of OP an increase of these inflammatory mediators is noticed [17]. Therefore, there are theoretical suggestions for the application of these medicines in OP therapy. One of the most commonly administered macrolides is clarithromycin. This antibiotic is characterised by its particular activity on Mycoplasma sp., Chlamydia sp., Legionella pneumophila, and many gram-positive and gram-negative bacteria. It also demonstrates unspecific anti-inflammatory efficacy, as mentioned above [17-20].

Taking into consideration the potential activities of CLA, this therapy was undertaken in patients with COP.

Material and methods

In the period from 1999 to 2005, 34 patients with OP were diagnosed in our department. Only 12 patients with cryptogenic form of OP, in good clinical status, were qualified to the prospective study. Five of these patients were presented earlier [21].

All patients were carefully clinically evaluated for additional diseases, consumption of medicines, symptoms and their duration. In addition, routine blood and urine tests, microbiological and immunological examinations of bronchoalveolar lavage were conducted. The presence of connective tissue disease, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, and serological tests for Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila were assessed. Additionally, adenovirus, cytomegalovirus, influenza and parainfluenza virus, respiratory syncytial virus and hepatitis virus (HBV, HCV) were investigated in selected cases. Chest X-ray and HRCT scan films were available in all the cases and were reviewed by two experienced radiologists. Two pulmonary pathologists analyzed all lung specimens independently. The following criteria were required for COP diagnosis: pulmonary infiltrations in radiological examinations suggesting organizing pneumonia, characteristic changes in lung biopsy specimens, negative microbiological and cytological analysis of BAL fluid, and exclusion of other causes of OP.

Patients were assessed every month during the treatment and re-evaluated at the end of it. Subsequently, in the first year, the patients were examined every 3 months and then every year.

Results

Nine women and 3 men, with an age range of 44–71 years, participated in the study. Two of them were smokers, 9 were non-smokers and one an exsmoker (tab. 1).

Goitre was an associated disease in 5 cases. One woman with Hashimoto disease had had a hypothyroidism for the past 25 years, and struma nodosa toxica was diagnosed in the time of investigation in another woman. One patient had COPD, 5 had hypertension and 4 had ischaemic heart disease.

Open lung biopsy was performed in 5 cases, and in 7 cases diagnosis was established on histological examination of specimens obtained by transbronchial lung biopsy.

Dyspnoea (100%), cough (100%), weakness (100%), fever (83%), loss of weight (83%), sweats (33%) and chest pain (8%), were the most common symptoms of OP. These symptoms preceded admission to the hospital by 1–6 months (mean 2.4 months).

All patients had radiological changes consistent with the typical pattern of bilateral interstitial infiltrates with air bronchogram. Additionally, in three cases, regions of densities of ground glass type were seen. The opacities were predominantly seen in peripheral parts of the lungs. Unilateral pleural effusion with hilar and mediastinal lymph node enlargement was observed in one case. Spontaneous migration of pulmonary infiltrates occurred in nine (75%) patients. Erythrocyte sedimentation rate (ERS) was elevated over 45 mm/h in all cases. Leucocytosis over 8,500/cc and eosinophilia over 600/cc mm were noticed in 8 and in 1 case/s, respectively. Significant elevation of antibody titers against Chlamydia pneumoniae and Mycoplasma pneumoniae in the IgG class of antibodies were detected in 5 and 1 patient/s, respec-

	No (%)
Gender	
Women	9 (75%)
Wen	3 (25%)
Age range	41–71 years
Smoking	
Non-smokers	10 (83%)
SHICKEIS	2 (17%)
Additional diseases	5 (/1%)
Hypertension	5 (41%)
COPD	1 (8%)
Atrial fibrillation	1 (8%)
Ischemic heart disease	4 (35%)
Biopsy	- / / / / /
Open lung biopsy	5 (41%)
Transbronchial lung biopsy	7 (59%)
Symptoms	10 (020/)
Fever	10 (83%)
Dysphoea	12 (100%)
Weakness	12 (100%)
Lose of weight	10 (83%)
Sweats	4 (33%)
Chest pain	1 (8%)
Duration of symptoms	1–6 months (mean 2.4)
RTX, HRCT	
Bilateral infiltrations	12 (100%)
Air bronchogram	12 (100%)
Migration	3 (23%) 9 (75%)
Pleural fluid	1 (8%)
Lymph nodes enlargement	1 (8%)
ERS > 45 mm/h	12 (100%)
WBC > 8500/cc	8 (66%)
VC < 80% predicted	5 (41%)
TLC < 80% predicted	3 (25%)
FEV1 < 70% predicted	5 (41%)
DLCO < 70% predicted	5 (41%)
$PaO_2 < 70 \text{ mm Hg}$	0
Observation period	3–90 months (mean 42 months)

tively. There were no changes in the concentration of these antibodies in the second examination (after 3 months); therefore, Mycoplasmal and Chlamydial infections were excluded. Anti-neutrophil cytoplasmic antibodies were negative in all examined patients, but in one man, without any symptoms of collagen vascular disease, the titer of anti-nuclear antibodies (ANA) was slightly elevated. During the course of the therapy ANA returned to normal values.

Bronchoscopy was performed in all cases. Bronchial wall inflammation was noticed in 4 pa-

tients and anthracotic scars were seen in one. In all cases, microbiological examinations of bronchial washings were negative for bacteria, acid fastbacilli and fungi. Bronchoalveolar lavage was performed in 6 cases. In 2 cases lymphocytosis was disclosed. Neutrophils were within normal limits in all cases, but in one patient a higher percentage of eosinophils was detected. A CD4/CD8 ratio of less than 0.7 was revealed in two patients.

In lung function tests the VC was reduced (less than 80% of predicted values) in 5 patients. In 3 of them TLC was also below 80% of the predicted values. Five patients had FEV1 decrease below 70% of predicted values. Restriction was revealed in 5 patients and obstructive pattern of ventilatory disorders was noticed in 1 COPD patient. Carbon monoxide diffusion capacity (DLCO < 80%pred) was decreased in 5 of 10 examined patients. There were no patients with hypoxemia (PaO₂ < 60 mm Hg; however, in 7 patients Pa0₂ was under 70 mm Hg.

Diagnosis of OP was established upon histological examination of transbronchial lung biopsy specimens (TBLB) in 7 cases and in 5 cases, on the open lung biopsy specimens (OLB). In all cases, polypoid masses of fibrous connective tissue within the small airways and alveoli, the infiltration of alveolar walls with inflammatory cells and preservation of alveolar architecture were seen. These findings were consistent with OP.

At the beginning all patients started CLA therapy in a dose of 0.5 g b.i.d. Nine (75%) patients were successfully treated. Complete clinical and radiological remission was obtained after 3 months of clarithromycin therapy in 7 patients, and partial response in 2 patients. During the first month of CLA treatment 3 patients did not improve; therefore, prednisone in a dose of 0.5 mg/kg/d was introduced. The complete recovery of these patients was seen after 6 months of corticotherapy. In 5 patients with very good results of CLA therapy in the third month of treatment the dose of this medicine was reduced to 0.25 b.i.d. Two patients with partial response were treated for an additional month but the dose was reduced to 0.25 b.i.d.

No adverse effects occurred due to CLA treatment. The observation period ranged from 30 to 90 months (mean 42 months) and no relapses were observed.

Discussion

COP has been a relatively rarely diagnosed disease. It is statistically estimated that idiopathic OP occurs in 6-7 people out of 100.000 hospitalizations [3, 4]. Lung biopsy is essential for OP diagnosis, so this might be the reason for its morbidity underestimation [2–4, 6, 8–15].

During the past 6 years 34 patients were diagnosed with OP in our department, and clarithromycin was administered to 12 of them. There was a preponderance of women in the group of our patients. In many series of patients men and women were equally affected by the disease, but in others there were a predominance of women [8–15]. It seems that COP is not related to smoking [3, 6, 11–15]. In our group of patients only two smokers were observed; however, Cazzato et al. reported over 50% of current smokers [8].

Thyroid disease was the most common concomitant disease in our patients. Watanabe et al. suggested a connection between thyroid disease and OP, and we paid special attention to this organ [22]. Probably thyroid disease might influence the development of OP, but hyperthyroidism was diagnosed only in one case during the time of investigation. Another 3 patients had slight inactive changes. A full examination of the thyroid gland is not in the spectrum of usual examinations of OP patients. Some thyroid diseases are obscure and asymptomatic; therefore, future studies are necessary to explain this phenomenon.

The onset of symptoms of COP is often subacute. Dyspnoea, weakness and cough were the most frequently noticed symptoms in all series of patients, as in ours [8–15]. The duration of symptoms in patients treated with CLA was shorter than in the other group of patients (2, 4 months vs. 4–7.5 months) [8–15]. Short therapy delay and good clinical status might influence good results of treatment. Lazor et al. suggested that delayed treatment increased the risk of relapse, but relapse did not correlate with clinical outcome [13].

The most typical radiological abnormalities of COP are bilateral, peripheral infiltrates with air bronchogram, which can migrate spontaneously. The nodular, focal or reticulonodular changes, pleural fluid and lymph node enlargement are seen rarely [8–15]. The chest X-ray and HRCT findings are sometimes characteristic and suggest the diagnosis, but differential imaging diagnosis with chronic eosinophilic pneumonias, lymphomas and bronchioloalveolar carcinoma is necessary [23]. A similar type of image, such as bilateral infiltrations with air bronchogram with areas of ground glass attenuation, was revealed in our patients, but migration of opacities was noticed in a rather high percentage of them.

The value of laboratory findings in diagnosing of COP is rather small [3, 4, 6, 8–15]. As in other inflammatory diseases, essential elevation of ESR and leucocytosis are observed. The main value of bronchoalveolar lavage is the exclusion of other causes of OP, particularly infections and neoplastic disorders. Bronchoalveolar lavage of COP patients is characterized by an increase in the number of lymphocytes, neutrophiles and eosinophiles, and a decrease in the CD4/CD8 ratio [3, 6, 9, 11, 13, 24]. Only 6 of our patients had undergone this procedure; therefore, it was not possible to draw any conclusions.

The ventilatory disorders noticed in our group of patients were not very severe. Lesions resulting in restrictive lung disease were shown in 5 cases. Airway obstruction occurred in 1 patient with COPD. In addition, 5 patients had decreased DLCO. Other researchers observed such disorders in over 60% of patients [6–14]. None of the analysed patients had hypoxemia, although in eight cases PaO₂ was less than 70 mm Hg. Watanabe et al. showed that hypoxemia was one of the important disturbances in patients with OP caused by intrapulmonary leak. This phenomenon was a negative factor for subsequent relapse [25].

Complete regression was achieved in 10 patients, and partial in 2 additional cases. Clarithromycin treatment was ineffective in 3 cases, the patients receiving prednisone in a dose of 0.5 mg/kg of body weight. No relapse was noticed. Treatment was usually continued for 3 months; however, in two patients with residual opacities in HRCT it was prolonged to 4 months. There were no adverse events caused by CLA. From such a small group it is very difficult to draw any conclusions regarding factors promoting good response to CLA. Undoubtedly, our patients were characterized by good clinical status and short period with symptoms; they did not have any severe ventilatory impairment or hypoxemia.

The beneficial specific and unspecific antiinflammatory effects of macrolide derivates were presented in many laboratory and clinical studies [17-20, 26-34]. Kudoh et al. demonstrated that erythromycin was effective in diffuse panbronchiolitis and significantly influenced the survival of those patients [26]. Itkin et al. and several Japanese studies have shown that macrolides diminished bronchial hyperactivity and had a steroid sparing effect in asthmatic patients [18, 20, 27]. In vitro examinations revealed that erythromycin increased neutrophil apoptosis and regenerated chlorine channels in patients with mucoviscidosis [17]. Except for antibacterial activity, this antibiotic inhibits biofilm formation, produced by Pseudomonas aeruginosa flagellin expression and adhesion to tracheal epithelium. It was shown that azithromycin and other macrolide derivates improved the FEV1 and VC, decreased the number of exacerbations and improved the quality of life in patients with mucoviscidosis [29, 30]. Long--term administered azithromycin decreased the frequency and intensity of bronchiolitis obliterans in patients after lung transplantation [31].

The efficacy of macrolide in OP has been presented in few studies. Ichikawa et al. reported 6 COP patients successfully treated with erythromycin for 3–4 months [32]. Arbetter et al. presented a case with radiation induced OP, with spontaneous improvement of pulmonary lesions, in whom an additional month of macrolide treatment was administrated [1]. Additionally, Epler et al. described an OP case treated by macrolide [33]. Recently Stover and Mangino published 6 cases of OP treated by clarithromycin [34]. Three cases were clinically cryptogenic and another 3 were related to radiation. The CLA therapy was effective in 4 patients. Two patients, after short courses of effective CLA treatment, relapsed and prednisone was subsequently introduced.

Examples of evidence that macrolides have specific and unspecific inflammatory activities and a beneficial effect in OP were presented in many data. Its use should be considered in treatment of COP patients.

Further studies regarding identification of patients who could potentially respond to clarithromycin are necessary.

Conclusions

Clarithromycin seems to be effective in selected patients with OP. This therapy is better tolerated than steroid therapy and does not produce serious adverse effects. It might constitute an alternative treatment in patients with OP.

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