Clarithromycin Stops Lung Function Decline in Airway-Centered Interstitial Fibrosis

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Abstract
Airway-centered interstitial fibrosis (ACIF) is a distinct type of lung interstitial fibrosis characterized by lesions centered on the airways. Several cases reported in the literature showed little to no effect of corticosteroids and a high mortality rate in the absence of lung transplantation. No other efficient approach is described for the treatment of this type of fibrosis. We report for the first time the case of a 44-year-old patient diagnosed with ACIF on surgical lung biopsy and stabilized with clarithromycin after failure of systemic corticosteroids. We need to confirm this benefit in other patients to ascertain the anti-inflammatory effect of macrolides in ACIF.

Key Words
Pulmonary fibrosis · Macrolides · Anti-inflammatory effect · Interstitial lung disease · Lung function decline

Established Facts
- Pulmonary fibroses are progressive and fatal lung diseases lacking effective treatment.
- Airway-centered interstitial fibrosis (ACIF) seems to be cortico-resistant, with inevitable loss of lung function and a high mortality rate in the absence of lung transplantation.

Novel Insights
- This is the first report of a patient diagnosed with ACIF and stabilized with clarithromycin after the failure of systemic corticosteroids.
- There is a need to confirm this benefit in other patients to ascertain the anti-inflammatory effect of macrolides in ACIF.

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Introduction

Airway-centered interstitial fibrosis (ACIF) is a distinct type of lung interstitial fibrosis characterized by lesions centered on the airways. Churg et al. [1] described 12 cases in 2004; these reports were followed by case studies from other authors [2–8]. Corticosteroids seem to have little to no effect, and the mortality rate is high in the absence of lung transplantation [1, 5, 7].

We report herein the first case of a patient diagnosed with ACIF stabilized with clarithromycin after the failure of systemic corticosteroids.

Case Report

A 44-year-old Caucasian patient with a smoking history of 10 pack-years who had stopped smoking 20 years prior and without a remarkable medical history or long-term medication was referred to our center because of progressive dyspnea and chronic bronchitis. He had bilateral crackles in both lower lung zones. No digital clubbing or extrathoracic finding was present. High-resolution chest CT scan showed predominant subpleural intralobular reticulations in both lung bases, associated with traction bronchiectasis and scissural distortion (fig. 1). Ground glass opacities were also found without honeycombing. Arterial blood gas analysis at rest in room air was normal. Pulmonary function tests (fig. 2) revealed a pure restrictive pattern with a TLC at 47% and FVC at 55% of the predicted values. The DLCO was decreased at 43% of the predicted values. The patient walked 560 m in 6 min in room air with a decrease in pulsed oximetry from 98% at rest to 86% after 6 min. No systemic inflammation (CRP = 2.3 mg/l), liver, renal or heart dysfunction was observed. Auto-immunity (anti-nuclear antibodies, ANCA, rheumatoid factors), HIV serology, and bird breeders’ and farmers’ lung serologies were negative. The bronchoalveolar lavage demonstrated 336,000 cells/ml with 75% macrophages, 9% neutrophils, 9% eosinophils, and 7% lymphocytes (41% CD4+/39% CD8+).

A surgical lung biopsy was performed (fig. 3) and showed interstitial fibrosis centered on membranous and respiratory bronchioles. Muscle hyperplasia was observed in the bronchiolar wall. No honeycombing or granulomatous lesion was observed; additionally, no polypoid plug was observed within the distal bronchioles. This disorder was very similar to the entity described by Churg et al. [1]; therefore, we considered ACIF as the final diagnosis.

The patient was treated with 1 mg/kg of oral prednisolone for 3 months in association with esomeprazole 40 mg/day without any efficacy. Prednisolone was then tapered progressively to 40 mg/day, and esomeprazole was continued at the same dose. The pulmonary function tests worsened during these treatments (fig. 2). Therefore, 6 months later, clarithromycin (500 mg/day for 1 month and then 250 mg/day) was initiated with a tapered dose of corticosteroids until reaching 20 mg/day as a maintenance treatment. The lung volumes improved slightly and then stabilized at 47, 44, and 47% for TLC, FVC, and FEV1, respectively, after 20 months of follow-up (fig. 2). No change in chest CT scan, arterial blood gases, DLCO, or a walking distance of 6 min was reported.

Discussion

This is the first description of a beneficial response to clarithromycin in a patient with ACIF. As environmental or occupational exposure is considered to be a strong risk factor for ACIF [1–4, 6–8], we carefully reviewed any exposure in our patient. We found only a mild smoking history (10 pack-years, cessation of smoking for 20 years). No animal contact, including contact with birds, was demonstrated.

Histology is the only method of diagnosis because the HRCT is nonspecific. Peribronchiolar reticulations and ground glass opacities associated with bronchiolitis on chest HRCT correspond to the pathological presentation with periairway fibrosis. As described by Colombat et al. [6], this airway centricity and the variable importance of the accompanying alveolar interstitial fibrosis indicate that the fibrosis process probably originates in the periairway tissue.

Churg et al. [1] treated the patients with prednisone (0.5–1 mg/kg/day) for 1–3 months followed by inhaled corticosteroids and inhaled bronchodilators as a long-term treatment or followed by progressive reduction toward a

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maintenance level of 5–15 mg/day [1]. Only 3 out of 12 patients improved with corticosteroids. The following cases described in the literature demonstrated the inefficacy of corticosteroids in this disease [5, 7, 8]. Azathioprine in addition to corticosteroids was used once without efficacy [8]. In contrast, cyclosporine and corticosteroid treatment demonstrated disease improvement in one case of clear bird-related hypersensitivity pneumonitis; in addition, allergen withdrawal was also performed in this case [4]. The only treatment described as efficient in ACIF was lung transplantation as reported by Colombat et al. [7].

Macrolide antibiotics appear to possess anti-inflammatory properties independent of their antibiotic effect and have been shown to be beneficial in a number of pulmonary disorders, mainly in diffuse panbronchiolitis, and in other chronic pulmonary inflammatory disorders, including cystic fibrosis, non-cystic fibrosis bronchiectases, chronic obstructive pulmonary diseases, and asthma [9]. Although the exact mechanism for the beneficial effect of macrolides has not been completely clarified, it is clearly not related to their antibiotic properties. Macrolides have been described to prevent airway epithelial...
damage and reduce mucus hypersecretion [10]. The immunomodulating effects of macrolides have been demonstrated; in particular, neutrophil accumulation, adhesion and apoptosis are clearly reduced, which results in markedly decreased airway neutrophilia [10]. Effects on cellular immunity with an impact on T-cell regulation and antigen presentation have also been demonstrated [10].

In summary, our case is the first report of ACIF showing a favorable response to treatment with clarithromycin. It will be necessary to confirm this benefit in other patients to ascertain this effect of macrolides, which have fewer side effects compared to immunosuppressant drugs, especially opportunistic infections.

References


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