Abstract

We report two cases in whom inhaled corticosteroid rapidly improved pulmonary sarcoidosis. In the first case, fluticasone at 400 μg/day was initiated, because dry cough and small nodular shadows on chest X-ray persisted for six months. But her cough and the nodular shadows were persisted, therefore the treatment was replaced with budesonide at 800 μg/day. Two months later, her dry cough subsided and pulmonary shadows improved. Serum angiotensin-converting enzyme (ACE) level was decreased and pulmonary function improved.

In the second case, bumethasone was already administered at a local clinic. Budesonide at 400 μg/day was combined with oral steroid, because pulmonary shadows continued for eight years. Also two months later, the serum ACE level was decreased and the pulmonary shadows slightly improved. Inhaled corticosteroid therapy for two to three months is tolerable, and may be a useful treatment option in some patients with sarcoidosis.

Key words: pulmonary sarcoidosis, inhaled corticosteroid

Introduction

Pulmonary sarcoidosis might lead to pulmonary fibrosis in some patients. Systemic administration of corticosteroid is performed; however, the indications are closely determined (1). Oral or intravenous corticosteroids have many adverse effects. In this study, we report two patients in whom inhaled corticosteroid markedly improved pulmonary sarcoidosis.

Patient 1

The patient was a 21-year-old woman. She was a non-smoker and given a diagnosis of rheumatoid arthritis (RA) at the age of 15 years. Non-steroid anti-inflammatory drugs were sometimes administered against RA. In March 2002, cough and sputum appeared, and diminution of vision was noted in July 2002. She consulted a local clinic, and chest X-ray showed an abnormal shadow; she was referred and admitted to our hospital. Concerning physical findings, palpation revealed superficial lymphadenopathy in the bilateral inguinal regions, and no rales were heard on auscultation. Laboratory tests showed an angiotensin converting enzyme (ACE) level of 77.6 IU/l (normal 8.6–21.8), a lactic acid dehydrogenase (LDH) level of 626 IU/l, a calcium level of 10.1 mg/dl, and a KL-6 level of 1,880 U/ml (normal <500). A lung function test showed that the PaO₂ and PaCO₂ were 102.6 Torr and 40 Torr, respectively. In addition, the VC, FEV₁, and DLco were 3,550 ml (110% of predicted), 3,040 ml (92% of predicted), and 18.5 ml/min/mmHg (94% of predicted), respectively. Neither electrocardiography nor echocardiography revealed any cardiac abnormalities, both showed normal wall thickness for the interventricular septum (6.5 mm) and left ventricle (7.5 mm) and a normal ejection fraction (74.4%). Chest X-ray and computed tomography (CT) showed swelling of the mediastinal and hilar lymph nodes and diffuse small nodular shadows in the bilateral lung fields (Fig. 1A, B). Ocular findings suggested uveitis. Under a tentative diagnosis of sarcoidosis, bronchoscopy was scheduled for the purpose of definitive diagnosis; however, it could not be performed due to lidocaine allergy. Inguinal lymph node biopsy revealed non-caseating epithelioid cell granulomas, and a definitive diagnosis of sarcoidosis was obtained. To treat the ocular lesion, administration of steroid eye drops was initiated, and the patient was discharged. The pulmonary lesions were fol-
allowed; however, exacerbation of the cough was observed, and administration of fluticasone propionate at 400 μg/day was initiated in October 2002, considering the sarcoidosis-related increase of airway hypersensitivity. In December 2002, the cough persisted, and there were no changes in the shadow on chest X-ray; therefore, the agent was switched to budesonide turbuhaler at 800 μg/day. In February 2003, the cough subsided, and in April 2003, chest X-ray showed marked improvement (Fig. 2). The serum ACE and KL-6 levels were decreased to 23.1 IU/l and 781 U/ml.

Figure 1. A) Chest X-ray showing bilateral hilar lymphadenopathy and diffuse small nodular shadows. B) Chest CT showing diffuse small nodular shadows in the peribronchovascular regions and interlobular septal thickening in both lungs.

Figure 2. A) Chest X-ray showing the markedly improvement of lymphadenopathy and nodular shadows after inhaled corticosteroid therapy. B) Chest CT showing the improvement both small nodules and septal thickening.
respectively. A lung function test showed that the VC, FEV₁, and DLco were increased to 3,840 ml (119% of predicted), 3,250 ml (98% of predicted), and 24.4 ml/min/mmHg (124% of predicted), respectively (Table 1). In September 2003, CT showed the disappearance of the small nodular shadows, and the serum ACE and KL-6 levels were within normal limits. Inguinal lymph node swelling had disappeared, with improvement in the ocular lesion. To date, maintenance therapy with budesonide at 400 μg/day is given.

### Patient 2

The patient was a 35-year-old woman. She was an ex-smoker until the age of 26 years (ten cigarettes per day for six years). She was given a diagnosis of uterocervical cancer in situ and laser therapy was performed at the age of 27 years. At the age of 25 years, she consulted the Department of Ophthalmology for ocular congestion, and was diagnosed as having uveitis. When she consulted a local clinic at the age of 26 years, chest X-ray showed bilateral hilar lymphadenopathy (BHL), and clinical findings suggested sarcoidosis. Bumethasone at 0.5 mg was administered every two days. When she moved to a new address, she was referred to our hospital, and was admitted for detailed examination in June 2000. Palpation did not reveal any abnormalities in the superficial lymph nodes, and no rales were heard on auscultation. The serum ACE level was 28.7 IU/l. A lung function test showed that the VC, FEV₁, and DLco were 2,780 ml (93% of predicted), 2,450 ml/ (85% of predicted), and 20.6 ml/min/mmHg (94% of predicted), respectively. Chest X-ray and CT showed BHL and diffuse nodular shadows (Fig. 3A). Transbronchial lung biopsy (TBLB) suggested non-caseating epithelioid cell granulomas, leading to a definitive diagnosis of sarcoidosis. After discharge, oral corticosteroid therapy was continued; however, there were no changes in the pulmonary shadow, and the serum ACE level remained at 27 to 30 IU/l. On a lung function test, the VC, FEV₁, and DLco values were decreased to 2,590 ml (87% of predicted), 2,290 ml (79% of predicted), and 17.9 ml/min/mmHg (81% of predicted), respectively. In May 2003, inhalation of budesonide at 400 μg/day was combined with steroid therapy. Two months later, the ACE level was decreased to 21.1 IU/l, with improvement in the pulmonary shadow (Fig. 3B). The VC,

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<th>Table 1. Pulmonary Function Tests and Serum Markers before and after Inhaled Corticosteroid</th>
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*Figure 3. A) Chest CT showing bilateral hilar lymphadenopathy, nodular peribronchovascular interstitial thickening and interlobular septal thickening. B) Chest CT showing slight improvement of lymphadenopathy and interstitial thickening.*
FEV₁ and DLCO values were 2,670 ml (90% of predicted), 2,340 ml (81% of predicted), and 18.0 ml/min/mmHg (82% of predicted), respectively, showing slight improvement (Table 1). In June 2004, the ACE level was normalized (14.2 IU/l), and the dose of bumethasone, an oral steroid, was gradually decreased to 0.25 mg/day, which was administered every two days.

Discussion

In the consensus statement regarding treatment for pulmonary sarcoidosis by the ATS/ERS/WASOG, it is recommended that systemic administration of corticosteroid should be indicated for patients with persistent pulmonary lesions or those in whom lung function is progressively reduced, even if there are no symptoms (1). In Patient 1, there were no changes in the chest X-ray, and the cough persisted for about six months. As the patient was a young female, an inhaled corticosteroid was initially administered, considering the adverse effects of systemic steroids. Budesonide improved the cough two months after the start of inhalation, and relieved the pulmonary shadow four months after the start of inhalation. Patient 2 had an eight-year history of sarcoidosis. Additional therapy of an inhaled steroid to an oral steroid improved the deteriorated thoracic shadow two months after the start of this therapy, with a decrease in the ACE level; therefore, the dose of the oral steroid could be gradually decreased. As sarcoidosis spontaneously subsides in some patients, it may be controversial whether or not the inhalation steroid achieved improvement in this patient. However, in Patient 1, we considered that not spontaneous improvement but the efficacy of the inhaled steroid had been achieved, as there were no changes in the symptoms or thoracic shadow for six months of follow-up. In Patient 2, combination therapy with the inhaled steroid achieved improvement, although there had been no changes for a few years. In addition, Patient 1 did not respond to fluticasone propionate, but a switch to budesonide achieved improvement, supporting the efficacy of the inhaled steroid. The particle diameter for budesonide turbuhaler is 3 μm, and the rate of pulmonary deposition is 30% (2); this agent may more efficiently reach the peripheral lung parenchyma compared to fluticasone propionate. The systemic effects of budesonide were less marked than those of fluticasone propionate (3), and no systemic effects appeared via a route other than the inhalation route. Reduction of the inguinal lymph node was observed, suggesting that the inhaled steroid influenced not only a local site but also the systemic immune response (4).

Several studies have reported inhaled steroid therapy for pulmonary sarcoidosis (5–10). In all studies involving single therapy with inhaled steroids, budesonide was employed; improvement in the laboratory data and symptoms/lung function was achieved in some studies (5, 6), whereas there were no changes in other studies (7). A consensus regarding the efficacy has not been obtained. In two studies in which inhaled steroids were employed for maintenance therapy following oral steroid therapy, improvement in the shadow and a decrease in the ACE level were observed (8, 9). In our patients, the interval from the start of inhalation until the appearance of effects was two to three months. Indications for the treatment of pulmonary sarcoidosis must be sufficiently examined; however, inhaled steroid therapy for two to three months is tolerable, and may be a useful treatment option.

References