INTRODUCTION

Pulmonary sarcoidosis is a common condition with an unpredictable clinical course. Oral corticosteroids are widely used in its treatment, but there is no consensus about when and in whom this therapy should be initiated, or about the ideal dose and duration of treatment [1].

Several serum markers have been shown to reflect the severity and progression of pulmonary sarcoidosis. Specifically, the serum levels of soluble interleukin 2 receptor (sIL-2R), lysozyme, and Krebs von den lungen-6 (KL-6) may reflect lymphocytic alveolitis [2]. Furthermore, the initial serum KL-6 level tends to be associated with increased parenchymal infiltration [2].

We present a patient with pulmonary sarcoidosis and high KL-6 level who showed marked improvement after initiation of high-dose inhaled budesonide.

CASE REPORT

A 48-year-old woman who had no subjective

Remarkable Improvement in Clinical Course and Serum KL-6 Levels after Initiation of High-Dose Inhaled Budesonide in Pulmonary Sarcoidosis

YOSHIKATA MORIMATSU *, **, MASAKI OKAMOTO*, TOMOTAKA KAWAYAMA *, YUSUKE MIZOGUCHI *, HARUKI IMAOKA *, HIDEO OGINO †, TAKETOSHI KAWAZU †, TATSUYA ISHITAKE ** AND TOMOAKI HOSHINO *

* Division of Respirology, Neurology and Rheumatology, Department of Internal Medicine,
** Department of Environmental Medicine, Kurume University School of Medicine, Kurume 830-0011,
† Shun-yokai Kawazu Internal and Respiratory Clinic, Hita 877-0061, Japan

Received 13 July 2016, accepted 17 January 2019
J-STAGE advance publication 1 May 2020
Edited by KOJI NAGAFUJI

Summary: We present a pulmonary sarcoidosis patient with specific elevation of serum Krebs von den lungen-6 (KL-6) levels, who was successfully treated with inhaled corticosteroids. Pulmonary sarcoidosis was initially identified as a chest radiograph abnormality during a routine medical examination, and subsequently confirmed by a high serum level of soluble interleukin 2 receptor. The patient was started on high-dose inhaled budesonide because of high serum levels of angiotensin-converting enzyme (ACE) and KL-6. Following treatment, radiographic findings improved, ACE levels normalized, and serum KL-6 levels markedly decreased. No recurrence was detected at 100 months with a budesonide dosage of 800 μg/day. This case demonstrates the efficacy of high-dose inhaled corticosteroids for the initial treatment of pulmonary sarcoidosis.

Key words pulmonary sarcoidosis, sarcoidosis-associated interstitial lung disease, KL-6, inhaled corticosteroid, budesonide, alveolar-capillary membrane permeability
symptoms and no smoking history was referred to us in January 2008 because of a chest radiographic abnormality noted during a recent medical examination. She was a social drinker and had no occupational exposure to dust or impaired vision. Laboratory tests showed an angiotensin-converting enzyme (ACE) level of 24 IU/L (normal 8.6–21.8) and a sIL2-R level of 1302 U/ml (Table 1). A transbronchial lung biopsy had been recommended prior to her referral, but she had refused. The patient later started smoking 0.2 pack per day from March 2008 to February 2010 (0.4 pack-years). She was admitted to our hospital due to enlarged mediastinal and bilateral hilar lymph nodes in April 2010. Her physical findings included late inspiratory fine crackles in both lung fields. The results of a lung function test were within normal limits (Table 1), and neither electrocardiography nor echocardiography revealed any cardiac abnormalities. Chest radiography demonstrated diffuse granular opacities and bilateral hilar lymphadenopathy (Fig. 1A). Chest computed tomography (CT) showed diffuse, small nodular opacities, interlobular septal thickening in both lungs, perilobular ground-glass opacities (Fig. 2A), and enlarged mediastinal and bilateral hilar lymph nodes (Fig. 2B). Ocular examination revealed no uveitis. Bronchoscopy demonstrated no abnormalities of the tracheal or bronchial mucosa. The recovery rate of bronchoalveolar lavage fluid (BALF) was 51.3% (77/150 ml) and the total cell count was 5.5 × 10⁵/ml, with 88.8% macrophages and 10.8% lymphocytes. At that point we recommended the administration of oral prednisolone, but the patient adamantly refused because she had previously developed a gastric ulcer when taking this medication. For this reason, inhaled budesonide was administered via a Turbuhaler, initially at 800 μg/day in May 2012. Chest radiograph after one month of treatment showed that ground-glass opacities in the lung fields and the mediastinal and bilateral hilar lymphadenopathy had begun to improve. However, the patient unilaterally discontinued the budesonide, leading to exacerbation of the lymphadenopathy. When she resumed the treatment, there was again a rapid decrease in ACE levels and improvement in the pulmonary opacities. This pattern repeated itself again at least twice. The budesonide dosage was increased to 1,600 μg/day approximately 16 months after the initial treatment (August 2013) as KL-6 levels increased and DLCO decreased, and serum ACE levels had decreased slightly. Six months after beginning this high-dose regimen the patient’s symptoms subsided considerably, and serum ACE levels were back to normal (Table 1). KL-6 levels decreased to pretreatment levels and DLCO increased (Table 1). Chest radiograph showed marked improvement of peribronchovascular thickening and bilateral hilar lymphadenopathy (Fig. 1C). CT demonstrated small peripheral areas of ground-glass opacity with interlobular septal thickening and peripheral bronchial dilatation (Fig. 2E). At 99 months after budesonide initiation, serum ACE levels were in the normal range and the KL-6 level was 1073 U/ml and the patient’s lung function had recovered to the level at first referral to us. To date, the patient is receiving maintenance therapy with inhaled budesonide at 800 μg/day and has shown no evidence of recurrence for 100 months.

DISCUSSION

KL-6 is expressed on type II pneumocytes in normal lung tissue, and serum KL-6 is specifically elevated in the majority of patients with interstitial lung diseases (ILDs) [3,4]. Serum KL-6 is presumably produced by regenerating type II epithelial cells at levels correlating with disease activity [3,4], and KL-6 is considered to be one of the most useful serum markers for monitoring disease activity in sarcoidosis [3,5]. On the other hand, several investigators have reported that levels of serum KL-6 reflect lymphocytic alveolitis and increased parenchymal infiltration [2,4]. In our case, elevation of serum KL-6 level is thought to be the result of sarcoidosis-associated peribronchial cell infiltration because CT findings revealed small opaci-
KL-6 DECREASED BY BUD IN SARCIOIDOSIS ILD

Fig. 1.
A: Chest radiograph obtained in January 2008 showing diffuse small nodular opacities and mediastinal and bilateral hilar lymphadenopathy.
B: Chest radiograph obtained in March 2012 showing enlarged, small, nodular opacities and swelling of the hilar lymph nodes.
C: Chest radiograph obtained in February 2014 showing marked improvement of both lymphadenopathy and nodular opacities after high-dose inhaled budesonide therapy.

Fig. 2.
A: Chest CT obtained in January 2008 showing diffuse, small, nodular opacities; interlobular septal thickening; slight bronchovascular bundle thickening; and peribronchial ground-glass opacities in both lungs.
B: Chest CT without contrast-enhanced obtained in January 2008 showing mediastinal and bilateral hilar lymphadenopathy.
C: Chest CT obtained in March 2012 shows peribronchovascular thickening and ground-glass opacities.
D: Chest CT with contrast-enhanced obtained in March 2012 shows increase in size of mediastinal and bilateral hilar lymph nodes compared with previous CT (Fig. 2B).
E: Chest CT obtained in February 2014 shows improvement of peribronchovascular ground-glass opacities, but a slight amount of interlobular septal thickening and peripheral bronchial dilatation are still depicted.
F: Chest CT obtained in February 2014 showing marked improvement of mediastinal and bilateral hilar lymphadenopathy.
ties, ground-glass opacities, and a thickened bronchovascular bundle [5]. Elevated levels in patients with ILDs are thought to result from increased local production of KL-6 and MUC1 in the lungs and enhanced permeability of the alveolar-capillary interface [3]. In sarcoidosis, increased levels of albumin in BALF are thought to result from an influx of plasma albumin into the alveoli [6]. Increased alveolar-capillary permeability is a highly sensitive marker of mild inflammation from any cause, and is prevented and reversed by steroid administration [7]. Long-term inhaled corticosteroids are likely to be useful if permeability is decreased [8]. In our case, high-dose inhaled corticosteroids may not only have reversed the increase in alveolar-capillary permeability, they may also have helped increase albumin levels in the alveoli. Alternatively, this treatment may have suppressed sarcoidosis-associated peribronchial cell infiltration. However, we must follow this patient up carefully as abnormal shadows still persist and the level of KL-6 is high.

Milman et al. evaluated whether high-dose inhaled steroids might be of therapeutic value in pulmonary sarcoidosis, but found no significant differences in the study variables between the budesonide and placebo groups [9]. Conversely, inhaled budesonide at a dosage of 1.200 μg/day showed clinical benefit with minimal adverse effects in patients with active pulmonary sarcoidosis [10], and when administered at this dosage for 6 months, significantly improved the clinical course of newly diagnosed pulmonary sarcoidosis relative to placebo [11]. However, further studies are necessary since the sample sizes in these studies were small.

Inhaled fluticasone treatment for pulmonary sarcoidosis was effective in 60% of patients with central lesions around thick bronchi, but was ineffective in patients with only parenchymal lesions [12]. On the other hand, some patients with parenchymal lesions were treated effectively with either budesonide or ciclesonide. Ohno et al. reported rapid improvement in a patient whose inhaled corticosteroid was switched from fluticasone 400 μg/day to budesonide 800 μg/day [13], indicating that budesonide may reach the peripheral lung parenchyma more effectively than fluticasone. These findings confirm that the lung parenchyma improves significantly more with budesonide treatment than with other corticosteroids.

Twelve randomized controlled trials of variable quality, involving 1051 participants, were reported in sarcoidosis [14]. Two studies showed no improvement in lung function, but in one study the diffusion capacity increased in the treated group [15,16]. Initial treatment with prednisolone, followed by long-term inhalation of budesonide, was more effective than placebo in patients with stage II disease [17], consistent with the finding in our patient, who responded well to an increased dose of inhaled budesonide. Different pulmonary lesions in sarcoidosis may respond variably to specific inhaled corticosteroids, but overall, this therapy may be an adequate treatment regimen for stage II sarcoidosis patients. Spiteri et al. found that inhaled steroids in pulmonary sarcoidosis acted directly at the cellular level via local anti-inflammatory activity [18]. In another study, beclomethasone dipropionate caused a decrease in the percentage of BALF lymphocytes, but this finding was based on a small number of patients with chronic sarcoidosis [19].

Inhaled corticosteroids may be the first choice for

| 2006.6 | 2008.1 | 2010.6 | 2012.3 | 2013.8 | 2014.2 | 2016.6 |
|--------|--------|--------|--------|--------|--------|--------|
| No symptoms | First visit | 3 months After Smoking cessation | BUD 800 μg start | BUD 1600 μg dose increase | BUD 800 μg | BUD 800 μg |
| ACE (IU/L) | 14.8 | 24 | 42.8 | 74.2 | 69.6 | 21.2 | 12.6 |
| KL-6 (U/ml) | 296 | – | – | 2596 | 4588 | 2641 | 1073 |
| VC (L) | – | 3.42 | 3.46 | 2.76 | 2.81 | 3.18 | 3.25 |
| %VC | – | 124.8 | 110.9 | 89.6 | 91.2 | 103.9 | 107.6 |
| FEV1.0 (L) | – | 2.46 | 2.61 | 1.79 | 2.09 | 2.70 | 2.77 |
| FEV1.0% | – | 72.4 | 77.7 | 65.8 | 76.0 | 88.2 | 86.0 |
maintenance therapy in pulmonary sarcoidosis, although additional studies with larger sample sizes are needed to further investigate this issue.

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