Churg-Strauss Syndrome after Reduction of Inhaled Corticosteroid in a Patient Treated with Pranlukast for Asthma

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Abstract

Recently, various forms of Churg-Strauss syndrome (CSS) have been reported in association with the use of leukotriene receptor antagonists. A 53-year-old woman with a 5-year history of asthma associated with chronic sinusitis presented mononeuropathy, hypereosinophilia, and positive P-ANCA in October 1999. She had been treated with pranlukast (450 mg/day) and beclomethasone dipropionate (BDP) at a dose of 1,200 µg/day which had gradually been tapered to 800 µg/day over the previous 17 months. She was found to have CSS, and 60 mg/day of prednisolone was administered instead of pranlukast, resulting in an improvement of her symptoms and eosinophilia. Later, we confirmed that serum P-ANCA had been positive before the pranlukast treatment, but CSS vasculitis had not appeared at that time. We speculated that an underlying incomplete form of CSS was being masked in this case and that the reduction of inhaled corticosteroid might have been responsible for the unmasking of CSS.

Case Report

A 53-year-old woman having a 5-year history of asthma associated with chronic sinusitis was referred to our hospital in March 1998 because of moderate asthma exacerbation. She had been treated for some unknown period time with inhaled corticosteroid (400–800 µg/day) and theophylline (200–400 mg/day) in conjunction with intermittent systemic corticosteroid (5–30 mg/day). Laboratory studies revealed eosinophilia of 2,960/mm³ (25.7% of her total WBC count) and a high serum IgE level of 1,470 IU/ml (upper limit of normal is 250 IU/ml). As shown in Fig. 1, she was treated as having moderate asthma exacerbation with oral prednisolone (PSL; 80 mg/day), theophylline (400 mg/day), inhaled β2-agonist and pranlukast (450 mg/day). Her symptoms gradually subsided, therefore inhaled beclomethasone dipropionate (BDP) was started instead of the oral PSL. BDP was continued at a dose of 1,200 µg/day initially and gradually tapered to 800 µg/day administered over a 17-month period. In early October 1999, she complained of numbness in the right foot. Electromyography was notable for right median and right peroneal neuropathy consistent with mononeuritis multiplex. The eosinophil count was 13,600/mm³ (58.5% of her total WBC count), the serum IgE level was up to 3,100 IU/ml and p-antineutrophil cytoplasmic antibody (P-ANCA) was 386 EU (normal limit is under 10 EU). Serum P-ANCA was measured in SRL Ltd laboratory (Hachioji, Tokyo) using a commercial enzyme-linked immunosorbent assay kit; NephroScholar. MPO-ANC (Nissho Co., Kusatsu, Shiga). No abnormal findings were revealed in chest roentgenogram. The patient was found to have CSS ac-
CSS Associated with Pranlukast

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- **PSL (mg/day)**: 80, 2.5, 60
- **BDP (µg/day)**: 1,600, 1,200, 800, 800
- **Pranlukast (450 mg/day)**: 1,600

**CSS vasculitis**

- **Eosinophils (/mm³)**: 2,955, 651, 1,790, 1,869, 3,366, 13,630, 26, 96
- **IgE (IU/ml)**: 1,470, 509, 856, 887, 940, 3,100, 356
- **P-ANCA (EU)**: 10, (-), (-)

**Figure 1. The clinical course. PSL: prednisolone, BDP: becromethasone dipropionate.**

According to the American College of Rheumatology Criteria (6). We could not perform skin biopsy because 60 mg of PSL had already been administered in the outpatient section. Peripheral blood lymphoproliferative responses to the content of pranlukast capsule were not observed at 6 concentrations (from 288 ng/ml to 900 µg/ml). After pranlukast discontinuation and treatment of PSL, her symptoms and the eosinophilia were resolved within 7 days, and serum P-ANCA became negative. A mild neuropathy still persisted in May 2000. Later, we confirmed that serum P-ANCA had been positive (10 EU) in the serum stored at −80°C in March 1998, but at that time CSS vasculitis had not appeared.

**Discussion**

This patient was found to have CSS associated with pranlukast, with positive serum P-ANCA. Only two similar CSS cases associated with pranlukast have been previously reported in the literature (7, 8). LRA was approved for use as asthma therapy and allowed significant reduction of systemic or high-dose inhaled corticosteroid administration, which in turn unmasked the underlying or unrecognized CSS (4, 5). Bili et al (9) also reported seven cases of CSS which were similar to those reported in association with LRA treatment, except that none of them had been receiving LRA. However, Green and Vayonis (3) reported the occurrence of CSS in association with zafirlukast in two patients who had not received systemic steroid treatment. In previous reports and our case (1–5, 7, 8, 10), the mean duration from the start of LRA to CSS onset in 3 LRAs were as follows: 3.2 months (n=11, 2–8 months) with zafirlukast, 4.3 months (n=6, 2–7 months) with montelukast, and 10.6 months (n=3, 4–17 months) with pranlukast. Pranlukast seemed to a need longer time for CSS to occur than the others, however the number of patients was too small. Further analysis of the pharmacological difference in each LRA is necessary to determine whether there are different effects in terms of unmasking the underlying and previously unrecognized (forme-fruste) CSS (11) among the three drugs.

One of the mechanisms for the development of CSS is allergic or idiosyncratic reaction to pranlukast. However, in the present case peripheral blood lymphocyte stimulation test using pranlukast was negative. Previous reports revealed that three different molecules of LRA, zafirlukast, montelukast and pranlukast caused CSS-like diseases. And recently, cases of CSS have also been reported to the US Food and Drug Administration in association with the use of the 5-lipoxygenase inhibitor, zileuton (12). It seems that the hypothesis of allergic or idiosyncratic reactions to pranlukast was not acceptable. Another possible mechanism is that the molecular or biological alteration of leukotriene receptor itself induced by LRA might cause CSS. This problem should also be further examined.

In general, serum P-ANCA is positive in 40–75% of patients with CSS. There has been no information about serum P-ANCA in cases of CSS associated with LRA and in particular as to whether P-ANCA had already been positive or not when LRA was administered. In the present patient, serum P-ANCA had been positive before the pranlukast treatment, but symptoms of CSS vasculitis had not yet appeared. On the other hand, Cohen et al (13) reported that prescreening for P-ANCA may not predict the development of CSS, but that nevertheless serum P-ANCA was a useful marker to assess the disease activity of CSS when it was positive. Actually, in our case, the level of P-ANCA was decreased in conjunction with CSS symptoms following PSL therapy.

We speculated that our case had the so-called forme-fruste CSS when pranlukast was started, because serum P-ANCA had
been positive and incomplete CSS symptoms existed at that time. On the other hand, Wechsler et al (5) reported a patient of CSS associated with montelukast with inhaled corticosteroid reduction, in whom no systemic steroid had been administered. It was unlikely that pranlukast was directly responsible for causing CSS in our case, but rather that the subsequent reduction in inhaled corticosteroid either unmasked or coincided with the natural course of a progressive preexisting condition of CSS.

References