

Asthma in pulmonary tuberculosis

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Key words: asthma; cytokines; infection; *Mycobacterium tuberculosis*.

● ACTIVE pulmonary tuberculosis infection has been known to induce the Th1 immune response (1) and may inhibit bronchial asthma characterized by the Th2 response (2) because it has been recognized that Th1 and Th2 cells are mutually exclusive and reciprocally regulated. We herein report the first case, to our knowledge, of well-controlled asthma following pulmonary infection with *Mycobacterium tuberculosis* in a patient with severe asthma.

On September 1997, a 21-year-old man visited our clinic for the management of severe persistent asthma with perennial symptoms for 5 years. He had normal chest radiographs, negative skin prick tests to common aeroallergens, and forced expiratory volume in 1 s (FEV₁) of 2500 ml (59% of predicted value). A significant change of $\geq 15\%$ in FEV₁ with inhalation of 400 μ g salbutamol was documented. He had frequent nighttime asthma symptoms. He received regular asthma medications, including inhaled long-acting β_2 -agonist (salmeterol 100 μ g/day), nedocromil sodium (8 mg/day), high-dose budesonide (1200 μ g/day), and sustained-release theophylline (400 mg/day). Oral prednisolone (40 mg/day) was added and was slowly tapered over 2 months. During the 2-month period, he consumed one canister of salbutamol (200 puffs per canister) as rescue medication, and the peak expiratory flow rate (PEFR) ranged from 420 to 650 l/min. After oral prednisolone was discontinued in December 1997,

he consumed more than one salbutamol canister per month even with regular asthma medications. In the beginning of April 1998, the patient's asthma symptoms became more aggravated by upper respiratory viral infection, with PEFR ranging between 190 and 550 l/min, and oral prednisolone (60 mg/day) was administered. Even with the appropriate medications, his asthma symptoms waxed and waned until January 1999.

In January 1999, he began to complain of anorexia, malaise, general weakness, low-grade fever, and night sweats. To his surprise, he had no asthma attacks and inhaled no salbutamol on demand. The asthma medications, except oral prednisolone, continued. At the end of February, a productive cough developed. On 4 March, chest radiographs showed extensive fibrostreaky and nodular densities in right upper-lung fields and other fibrostreaky densities in left mid-lung fields. Microscopic acid-fast bacilli were found in sputum. Sputum culture identified *M. tuberculosis*. On 10 May, an antituberculosis regimen were begun, including isoniazid, rifampin, ethambutol, and pyrazinamide. The tuberculosis responded to the medications well. The chemotherapy was successfully completed in February 2000. Until the end of October 1999, his asthma was very well controlled by the asthma medications, without oral prednisolone, and he was very satisfied with his asthma care. PEFR ranged from 530 to 600 l/min.

After November 1999, however, the patient's asthma returned to the condition of poor control, although the doses of asthma medications did not change. He inhaled at least one canister of salbutamol per month, with PEFR ranging from 180 to 580 l/min. After the completion of the tuberculosis treatment, oral prednisolone (30 mg/day) was administered. He has since visited our clinic on a regular basis for asthma control.

In our interesting case, a possible explanation for the control of asthma after tuberculosis infection could be that the Th1 immune response induced by infection with *M. tuberculosis* (1) suppresses the ongoing inflammatory process of bronchial asthma characterized by the Th2 response (2). Furthermore, the fact that asthma returned to the condition of poor control after the well-controlled 9-month period following the tuberculosis infection may reinforce the suppressive effect of active pulmonary tuberculosis on asthma, a conclusion which may be supported by a study (3) reporting that the degree of T-cell activation lessened upon completion of a 6-month course of anti-tuberculosis chemotherapy in active pulmonary tuberculosis. However, the above explanations should warrant further investigations. In addition, asthmatic patients on oral steroids should have regular routine chest radiographs to detect pulmonary infections such as tuberculosis earlier.

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Rofecoxib as an alternative in aspirin hypersensitivity

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Key words: aspirin intolerance; cyclooxygenase-2 inhibitor; NSAID; rofecoxib; urticaria.

• THE mechanism underlying intolerance reactions to nonsteroidal anti-inflammatory drugs (NSAID) is not well understood. The clinical picture resembles a type I reaction (Coombs and Gell) including conjunctivitis, rhinitis, shortness of breath, angioedema, hypotension, and, in severe cases, even shock. It is assumed that the pathogenetic mechanism is IgE-independent, since intolerance reactions can be induced by NSAIDs of different chemical structures, and specific IgE directed against NSAIDs is only rarely detectable. Inhibition of the central enzyme in the arachidonic acid pathway, cyclooxygenase (COX), by several NSAIDs may be essential for the development of an intolerance reaction, since it leads to an increased synthesis of leukotrienes (LT) with bronchoconstrictory capacities (LTC₄, LTD₄, and LTE₄) (1). Unfortunately, only a limited number of alternative anti-inflammatory pain

medications can be offered to aspirin-intolerant patients. Accordingly, the selective COX-2 inhibitors celecoxib and nimesulid have been conclusively reported to prevent pulmonary symptoms in aspirin-sensitive asthmatics. We here report the first case of an aspirin-intolerant patient who, upon oral challenge with aspirin, but not with the selective COX-2 inhibitor rofecoxib, developed severe cutaneous and extrapulmonary mucosal symptoms.

A 39-year-old patient was referred to our department with a history of rhinitis, swelling of the nasal mucosa, conjunctivitis, and shortness of breath 30 min after ingestion of 25 mg dexketoprofen. The patient denied having asthma, drug intolerance, or other allergies in the past. Acetylsalicylic acid (aspirin)- or pyrazolone-specific IgE antibodies in the serum could not be detected. Prick testing of a standard series with different NSAIDs in addition to dexketoprofen was negative. On the first day of the study, oral challenge with increasing amounts of the selective COX-2 inhibitor rofecoxib (suspensions of 1.2, 3, and 6 mg) given every 30 min was well tolerated, and 2 days later, oral challenge with 20, 50, and 125 mg of aspirin given at 30-min intervals was tolerated without complications. However, 20 min after challenge with aspirin at a dose of 250 mg, the patient developed itching of the eyelids and nasal mucosa, conjunctivitis, and generalized urticaria. Drug intolerance to aspirin was diagnosed and intravenously treated with 250 mg methylprednisolone and 2 mg clemastine hydrochloride.

Although the pathogenetic mechanism of NSAID intolerance is still incompletely understood, there are several reasons supporting the hypothesis that the enzyme COX and leukotrienes may play a crucial role. First, a mutation in the gene encoding the LTC₄ synthase results in increased levels of bronchoconstrictory LTC₄ in the

bronchoalveolar lavage of aspirin-intolerant asthmatics (2). Secondly, bronchospasm due to NSAID intolerance in asthmatics can be successfully treated with leukotriene receptor antagonists and lipoxygenase inhibitors (3). Third, it has been recently reported that the selective COX-2 inhibitor celecoxib did not induce bronchospasm in 27 aspirin-intolerant asthmatic patients (4).

We here provide evidence that the selective COX-2 inhibitor rofecoxib is well tolerated in a patient with aspirin intolerance and mainly extrapulmonary symptoms such as urticaria, rhinitis, and conjunctivitis. Thus, the new class of selective COX-2 inhibitors may be a useful alternative in the anti-inflammatory treatment for patients with arthritis and NSAID intolerance.

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