

Clinical Communications

A case of lactoferrin-induced occupational asthma

Kiho Shinagawa, MD^a, Chiyako Oshikata, MD^{a,b},
Takeshi Kaneko, MD^b, and Naomi Tsurikisawa, MD^{a,b}

Clinical Implications

- We present a novel case of occupational lactoferrin-induced asthma. A 43-year-old Japanese man experienced asthma symptoms after a year of work adding lactoferrin powder to a tank. His asthma decreased with exposure avoidance and ultimately disappeared.

Despite the lack of a worldwide epidemiologic study of cow's milk allergy, its reported prevalence during infancy has ranged from 1.9% in a Finnish study, 2.16% on the Isle of Wight, 2.22% in Denmark, 2.24% in the Netherlands, and as high as 4.9% in Norway.¹ Cow's milk protein consists of approximately 80% casein and 20% whey protein. Whey protein contains β -lactoglobulin 10%, α -lactalbumin 4%, proteose peptone 4%, and lactoferrin at levels as low as approximately 2%.

Asthma caused by cow's milk has been reported; the allergens are often casein and β -lactoglobulin. Seven cases of occupational asthma due to casein were reported in journals from 1990,² and 3 cases of occupational asthma due to α -lactalbumin were reported from 1994.³ To our knowledge, there have been no reports of occupational asthma caused by inhalation of lactoferrin or β -lactoglobulin. Here, we present what we believe to be the first report of occupational asthma caused by lactoferrin.

A 43-year-old Japanese male ex-smoker (Brinkman index: 35) presented with a history of allergic dermatitis since age 2. In addition, he had developed pediatric asthma at age 10 but had no family history of asthma, although his mother did have a pollen allergy. By age 17, the man was having asthma attacks due to cold, exercise, or seasonal change several times a month. After age 18, his asthma attacks had decreased to several times a year. However, he later experienced an increase in asthma exacerbations to several a month and had been taking fluticasone plus salmeterol (250 + 50 mcg) twice daily since age 35.

Since the age of 40, the man had worked putting milling bags of lactoferrin powder into a large tank to make a lactoferrin supplement. At age 41, he experienced a first episode of paroxysmal dyspnea, cough, nasal discharge, nasal congestion, and itchy eyes or skin 30 minutes after working with lactoferrin. He had no asthma attacks, runny nose, or pruritus outside working hours. He had no asthma attacks when he drank milk.

We found that the lactoferrin supplement contained lactoferrin (derived from cow's milk), crystalline cellulose, shellac, carboxymethylcellulose sodium-Ca, sucrose ester, fine silicon oxide, arginine, sorbitol, lactose, dextrin, and *hihatsu* (long pepper) extract. We obtained written informed consent from the patient to perform skin prick tests and bronchial provocation tests against cow's milk, *hihatsu* extract, the lactoferrin supplement, and lactoferrin powder. We performed a skin

prick test and measured antigen-specific serum IgE levels, as described. A positive reaction was defined as specific IgE > 0.35 IU/mL serum. We received the lactoferrin supplement and *hihatsu* extract from the patient's workplace, and we purchased purified lactoferrin powder (Morinaga Milk Industry Co., Ltd., Tokyo, Japan) and cow's milk (Torii Pharmaceutical, Tokyo, Japan). We evaluated the wheal and flare sizes 15 minutes after pricking of the skin with these antigens, compared with the sizes after positive control skin pricking with histamine.⁴ The patient had positive reactions to both lactoferrin supplement (22 × 5 mm) and lactoferrin powder (34 × 15 mm), compared with 11 × 10 mm after the histamine skin prick and negative reactions to both cow's milk (6 × 3 mm) and *hihatsu* extract (0 × 0 mm). We tested lactoferrin supplement, lactoferrin powder, and *hihatsu* extract on the skin of 6 healthy individuals and confirmed that there was no nonspecific reaction.

The serum total IgE level was 7710 IU/mL (normal range, 173 or less). Antigen-specific serum IgE was detected at 20.70 UA/mL for cow's milk, 1.84 UA/mL for casein, 0.50 UA/mL for α -lactalbumin, and 0.35 UA/mL for β -lactoglobulin. In an allergen component analysis (immunoCAP ISAC test; Phadia Multiplexing Diagnostics GmbH, Vienna, Austria), the Bos d (*Bos domesticus*) lactoferrin test, as an indicator of the lactoferrin-specific serum IgE level, was positive at class 2 (1.3 ISU-E, where ISU represents ISAC standard units). However, the Bos d 8 test for IgE to casein was negative.

There were no abnormal findings on chest radiography. The patient had minor airway impairment and airway reversibility. His spirometry parameters when not experiencing acute asthma exacerbations were exhaled nitric oxide concentration, 40 ppb; vital capacity, 4.02 L; percent-predicted vital capacity, 105.5%; forced expiratory volume in 1 s (FEV₁), 3.20 L; percent FEV₁, 88.3%; maximum expiratory flow rate at 50% forced vital capacity (FVC), 3.91 L/s; percent maximum expiratory flow rate at 50% FVC, 72.6%; and increase in FEV₁ 30 minutes after inhalation of β -agonist, 0.29 L.

We performed bronchial provocation tests with lactoferrin supplement or lactoferrin powder, or with saline as a negative control, in accordance with the method of Arvidsson et al.⁵ We prepared antigen concentrations as follows: 0.001 g/mL, 0.01 g/mL, or 0.1 g/mL of lactoferrin supplement, or 0.002 g/mL, 0.02 g/mL, or 0.2 g/mL of lactoferrin powder. Bronchial provocation testing was performed by using a nebulizer (DeVilbiss 646; DeVilbiss Co., Somerset, PA) with tidal breathing for 2 minutes. The operating airflow of this device was 5 L/minute. Isotonic saline was inhaled first as a control. Increasing concentrations of lactoferrin supplement or lactoferrin powder were then inhaled until the FEV₁ fell by >20% of its post-saline value or until the maximum lactoferrin supplement or lactoferrin powder concentration was reached. The interval between supplement testing and powder testing was at least 2 months.

Ten minutes after antigen-specific provocation with 0.001 g/mL of lactoferrin supplement or 0.002 g/mL of lactoferrin powder, the patient developed wheezing, chest tightness, and an itchy throat; his FEV₁ decreased from 3.45 to 2.13 (61.7% of the pre-provocation FEV₁) with lactoferrin supplement and from 3.51 to 2.73 (77.8% of the pre-provocation FEV₁) with

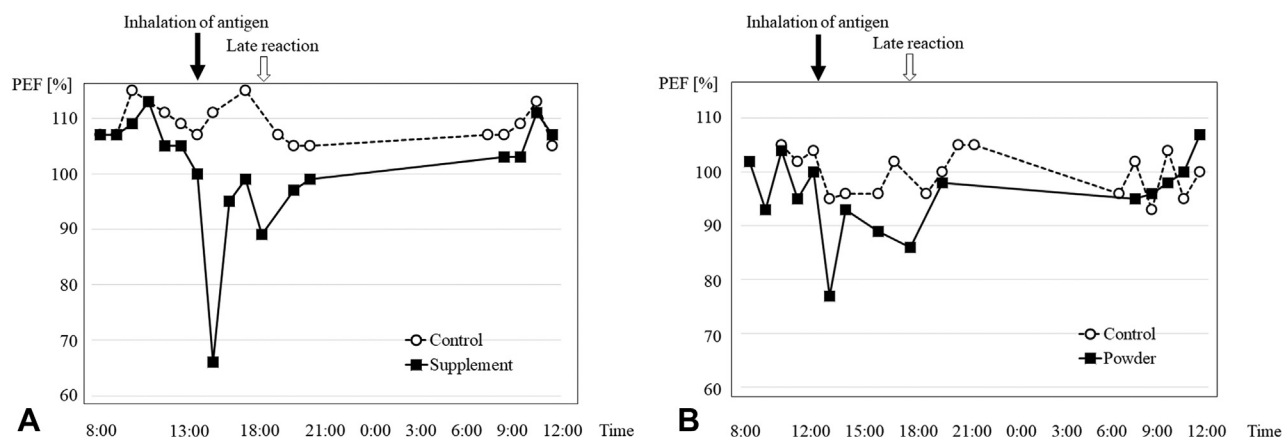


FIGURE 1. Bronchial provocation in the patient by using 0.001 g/mL of lactoferrin supplement (A) or 0.002 g/mL of free lactoferrin powder (B) (solid squares). Open circles are negative control antigen. The changes in peak expiratory flow (PEF, %) over 10 to 60 minutes from baseline (100%) were recorded. A decrease of >20% represented a positive reaction to the provocation protein fraction. The white arrow indicates late reaction 5 hours (A) or 6 hours (B) after provocation.

lactoferrin powder. Peak expiratory flow (PEF) decreased to 65.8% (Figure 1, A) or 76.8% (Figure 1, B) of that preprovocation 10 minutes after the provocation. The patient also experienced a late reaction of wheezing or chest tightness at 5 hours (Figure 1, A) or 6 hours (Figure 1, B) after antigen provocation. We did not actually test the higher doses because of these low-dose reactions. We diagnosed this patient with occupational asthma caused by lactoferrin.

Thereafter, the patient avoided exposure to lactoferrin by wearing a mask, goggles, and gloves when working. His asthma attacks decreased, and his other symptoms (nasal discharge and itchy eyes or skin) abated. Moreover, the patient has not experienced any asthma symptoms for 8 months since he changed his work and workplace from handling lactoferrin to security work. His serum total IgE level had decreased from 7710 UA/mL to 5880 UA/mL 8 months after the start of allergen avoidance. His specific serum IgE level to cow's milk decreased from 20.70 UA/mL to 7.98 UA/mL, to casein from 1.84 UA/mL to 1.63 UA/mL, to α -lactalbumin from 0.50 UA/mL to 0.33 UA/mL, and to β -lactoglobulin from 0.29 UA/mL to 0.72 UA/mL.

Lactoferrin is well known as an immune substance contained in breast milk, and in recent years, lactoferrin has received attention for its antibacterial action and its potential roles in preventing metabolic syndrome and asthma attacks.⁶ However, the Bos d lactoferrin antibody positivity rate is 50% in infants with atopic dermatitis with cow's milk allergy.⁷ In animal experiments, acetylcholine airway hyperresponsiveness has been enhanced in mice after intraperitoneal sensitization to human lactoferrin and inhalation exposure by nasal instillation.⁸ Because lactoferrin is rapidly hydrolyzed and inactivated by pepsin under acidic conditions, it does not become an allergen when ingested. In the presented case, the lactoferrin powder induced an allergic reaction in the nasal mucosa and respiratory tract, but oral administration of cow's milk did not.

Bronchial provocation tests with inhalation of allergen were reported as early reactions in 1873 and late reactions in 1951.⁹ FEV₁, the standard end point for measurement in most bronchoprovocation studies with allergens or other substances, was established in the late 1950s. The antigen provocation test has a

long history, and many papers have reported on it; it is safe because it is performed by a standard method using spirometry. We evaluated FEV₁ as an early reaction and PEF as a late reaction; because the patient could easily measure PEF at home, we used it for measurement after the load test. Because we were able to diagnose asthma in this patient through airway reversibility testing, airway hypersensitivity testing with methacholine was not performed.

We think that the total IgE level was high because this patient was positive for many antigen-specific IgE antibodies other than cow's milk, casein, and α -lactalbumin, namely allergens such as house dust mite, fungi, pollen, and pets. The decrease in milk-specific IgE antibody titers after 8 months likely occurred because inhalation of lactoferrin as a component of milk was stopped.

It is possible that allergic disease, such as asthma or atopic dermatitis, was the mechanism behind this patient's occupational asthma due to lactoferrin, but it is equally possible that the prolonged and abundant antigen exposure that occurs in some occupations can, albeit rarely, result independently in asthma. This patient's symptoms of asthma and atopic dermatitis decreased after antigen avoidance. We consider this case valuable because it is important to recognize lactoferrin as an occupational allergen.

^aDepartment of Allergy and Respiriology, Hiratsuka City Hospital, Hiratsuka, Kanagawa, Japan

^bDepartment of Pulmonology, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan

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Corresponding author: Naomi Tsurikisawa, MD, Department of Allergy and Respiriology, Hiratsuka City Hospital, 1-19-1 Minamihara, Hiratsuka, Kanagawa 254-0064, Japan. E-mail: User831328@aol.com.

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