

Occupational Asthma Related to Mouse Allergen Exposure and Rhinoconjunctivitis due to Collagenase Inhalation in a Laboratory Technician

X. Muñoz^a S. Gómez-Ollés^b M.J. Cruz^b F. Morell^b

^aServicio de Neumología, Hospital Vall d'Hebron, Departamento de Biología Celular, Fisiología e Inmunología, Facultad de Medicina, Universidad Autónoma de Barcelona, ^bServicio de Neumología, Hospital Vall d'Hebron, Barcelona, Spain

Key Words

Occupational asthma · Collagenase · Mouse proteins · Specific inhalation challenge

Abstract

We describe the case of a 27-year-old patient working in a research laboratory, who developed occupational asthma to mouse proteins and presented symptoms of rhinoconjunctivitis caused by manipulation of collagenase. Specific inhalation challenge confirmed the diagnosis of occupational asthma to mouse proteins, whereas specific challenge with collagenase only evoked symptoms of rhinitis and conjunctivitis. SDS-PAGE and Western blot analysis for collagenase showed that the patient's IgE antibodies bound specifically to a protein with a molecular weight of 92 kDa. Hence, this was an unusual case of double sensitization. The sensitization to collagenase presented in this report may represent a new occupational disease in technicians working in medical or research laboratories.

Copyright © 2005 S. Karger AG, Basel

Introduction

Occupational respiratory allergy and occupational asthma (OA) caused by exposure of workers to proteolytic enzymes has been extensively described [1–3]. These enzymes, which are mainly used in the manufacture of detergents and in the food and pharmaceutical industries, have highly allergenic properties [4]. Occupational respiratory allergy and asthma have also been described in medical laboratory technicians involved in the use of proteolytic enzymes, such as pepsin, trypsin, pectinase or papain [5, 6]. However, proteins from rat and mouse urine are among the most highly implicated agents in the genesis of occupational respiratory disease in this population [7, 8].

In contrast to nonoccupational asthma and rhinitis, in which there may be multisensitization [9, 10], there are few reports describing an association between two or more agents causing sensitization and secondary respiratory problems in occupational respiratory disease.

We report the case of a laboratory technician who developed double sensitization, presenting rhinitis and conjunctivitis after contact with powdered collagenase, an enzyme that has not been described previously as a cause of respiratory symptoms, and OA due to contact with mouse allergens.

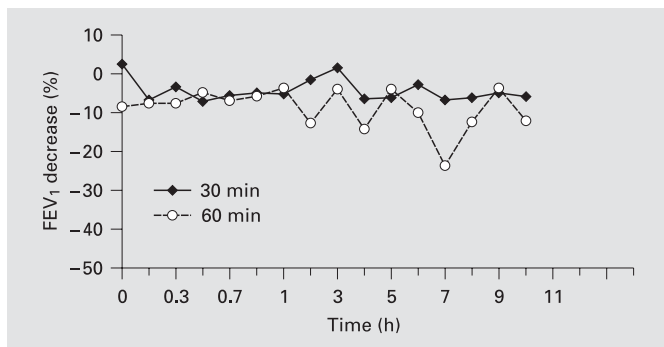


Fig. 1. Specific inhalation challenge by exposing the subject to mouse proteins for 60 min. A late asthmatic reaction with a significant fall in FEV₁ was noted 7 h after the test.

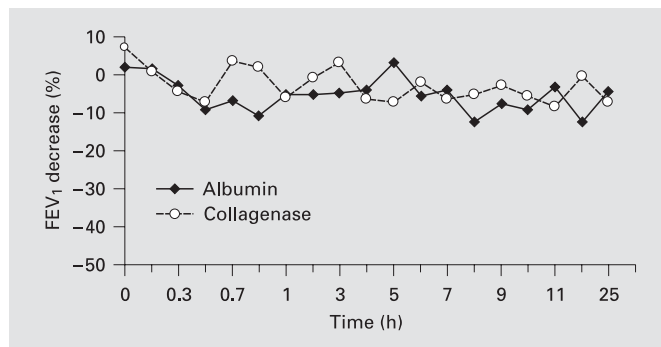


Fig. 2. Results of specific inhalation challenge with collagenase. No significant changes in FEV₁ were observed. Nevertheless, symptoms of rhinitis and conjunctivitis manifested during the test.

Case Report

A 27-year-old woman, with no toxic habits or medical history of interest, had been working for 3 years in a diabetes research laboratory. The patient consulted for episodes of rhinitis and exertional dyspnea of 2.5 years' evolution. The symptoms were related to work and, specifically, to the manipulation of collagenase used in her laboratory's study protocols (Collagenase P, Roche Diagnostics GmbH, Penzberg, Germany), and to exposure to mice in the animal facilities. The patient was in contact with mouse allergens virtually every workday, whereas collagenase exposure occurred every 5–7 days. The collagenase powder was weighed and used to digest mouse pancreas tissue in order to isolate islets of Langerhans. The patient's symptoms appeared at the end of the working day and generally improved on the weekend and during vacation periods.

Physical examination and the chest X-ray at the time of consultation were normal. Blood tests showed 5,800 leukocytes with 7.9% eosinophils and a total IgE value of 83 kU/l. Tests for specific IgE to mouse allergens, including epithelium, serum proteins and urine proteins (UniCAP System; Pharmacia AB; Uppsala, Sweden), were negative. Skin prick tests to common pneumoallergens were negative and pulmonary function study showed the following: FVC 3,960 ml (89%), FEV₁ 3,320 ml (93%) and FEV₁% 83%, with negative bronchodilator testing. The methacholine test showed a PC20 of 8 mg/ml. Maximum expiratory flow recorded for 2 weeks while the patient was working and 1 week outside of the workplace was not consistent with OA. Specific inhalation challenge (SIC) to mouse proteins was performed, with the patient undergoing prolonged exposure lasting 30 and 60 min on successive days inside the animal facilities, where 100 mice were housed. The test was positive, with a delayed response after 60 min of exposure manifested as a 24% fall in FEV₁ at 7 h after the test (fig. 1). The patient was diagnosed with OA due to mouse allergens and was advised to discontinue work in the animal facilities. In the following months, the patient did not present pulmonary symptoms, but the rhinitis persisted and episodes of conjunctivitis occurred whenever she manipulated collagenase. SIC to collagenase was performed with negative results for asthma (fig. 2), although symptoms of rhinitis and conjunctivitis were reproduced during the test. During the SIC the patient manipulated collagenase during 5 min inside a bronchial challenge

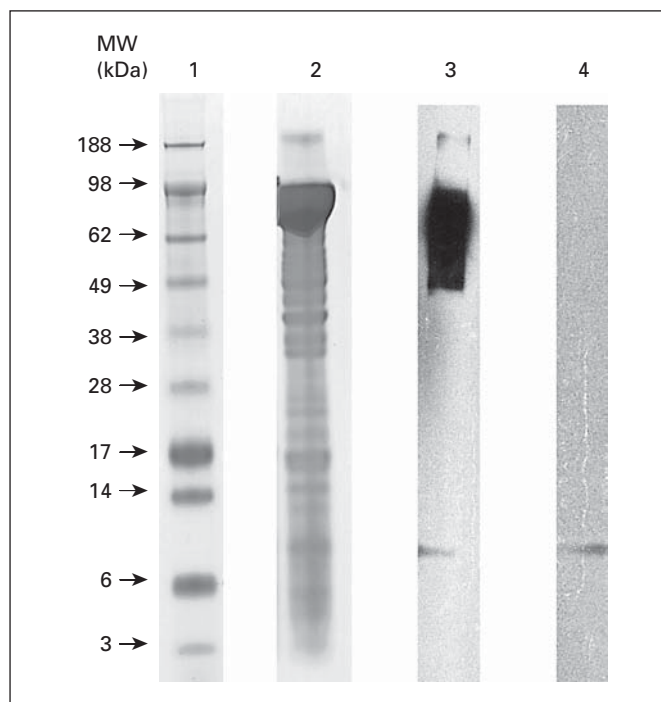


Fig. 3. SDS-PAGE and immunoblotting results. Lane 1: MW markers; lane 2: SDS-PAGE of collagenase extract; lane 3: immunoblotting of patient serum (IgE demonstrated intense binding to the collagenase protein), and lane 4: immunoblotting of control serum (no bands were found in serum from one control subject).

booth, simulating her usual work conditions. Specific IgE antibodies to the collagenase used in the patient's work were determined by SDS-PAGE and Western blot analysis. IgE antibodies from the patient's serum recognized a band of proteins of 92 kDa (fig. 3). After receiving the diagnosis of occupational rhinoconjunctivitis due to collagenase and recommendations to avoid exposure to this agent, the patient remained asymptomatic for the following 12 months.

Discussion

We report a case of double sensitization to mouse allergens and collagenase in a laboratory technician. Although sensitization to proteolytic enzymes has been extensively reported in the literature [1–3], to our knowledge, there is no published description of sensitization to collagenase. Hence, this is the first time that serum IgE antibodies against this proteolytic enzyme have been demonstrated. The manifestations in our patient included respiratory symptoms of rhinitis and conjunctivitis, as has been reported in other cases of allergy to proteolytic enzymes [11, 12]. Our patient also referred to symptoms consistent with asthma; however, these were shown to be attributable to exposure to mouse proteins and not to collagenase.

On the basis of the patient's symptoms and occupation, OA and rhinitis due to exposure to mouse proteins was initially suspected. The studies carried out, including SIC, confirmed this hypothesis, with a late response in the SIC. Although early responses are the most common in this type of asthma, a late response can occur as an isolated event 4–12 h after exposure [13]. The patient did not present specific IgE antibodies to mouse allergens, but other authors have reported similar findings. In a study performed in laboratory workers exposed to rats, Lieutier-Colas et al. [14] found that only 30.8% of all the symptomatic subjects enrolled were sensitized to rat allergens. Consistent results were suggested by Platts-Mills et al. [15] who reported that only 63% of symptomatic patients had specific IgE to rat urinary allergens. However, these findings may be due to the fact that the extracts used to perform the measurements might not have detected all the sensitized subjects [14].

The persistence of symptoms after antigenic exposure to mouse proteins was discontinued and coinciding with

exposure to collagenase led to the suspicion that this agent might also be involved in the patient's symptoms. This fact was confirmed by the SIC, in which symptoms of rhinitis and conjunctivitis were reproduced without decreases in FEV₁ values (fig. 2), and by positive specific IgE results obtained by SDS-PAGE and Western blot analyses. After discontinuation of collagenase exposure, the symptoms have not returned.

In addition to the first evidence of collagenase sensitization, the case presented underscores the possibility of double sensitization having an occupational origin. Patients with asthma and rhinitis often show multiple sensitization [9]; nevertheless sensitization of this type has been infrequently reported in respiratory disease of occupational origin. The sporadic cases described concern cross-reactive allergens, as occurs between isocyanates or metals [16, 17] and between some enzymes [2, 18, 19]. The possibility of presenting double or multiple sensitivity against unrelated antigens is rarely cited. Santaolalla et al. [20] described a case of double sensitization to fungal α -amylase and egg lysozyme in a baker, and Lee et al. [21] reported a case of OA and rhinitis caused by multiple herbal agents in a pharmacist. The double sensitization in our patient was probably not due to an atopic state, because the levels of total IgE were low and skin prick tests to common pneumoallergens were negative.

In conclusion, it is important to emphasize that in patients with occupational respiratory disease exposed to more than one possible sensitizing agent, multiple sensitization should be suspected when symptoms do not improve after exposure to the antigenic source is discontinued. The collagenase sensitization presented in this report may represent a new occupational disease in technicians working in medical or research laboratories.

References

- 1 Baur X, Sander I, Posch A, Raulf-Heimsoth M: Baker's asthma due to enzyme xylanase: a new occupational allergen. *Clin Exp Allergy* 1998; 28:1591–1593.
- 2 O'Connor TM, Bourke JF, Jones M, Brennan N: Report of occupational asthma due to phytase and β -glucanase. *Occup Environ Med* 2001;58:417–419.
- 3 Sarlo K: Control of occupational asthma and allergy in the detergent industry. *Ann Allergy Asthma Immunol* 2003;90(5 suppl 2):32–34.
- 4 Schweigert MK, Mackenzie DP, Sarlo K: Occupational asthma and allergy associated with the use of enzymes in the detergent industry: a review of the epidemiology, toxicology and methods of prevention. *Clin Exp Allergy* 2000; 30:1511–1518.
- 5 Kempf W, Oman H, Wüthrich B: Allergy to proteases in medical laboratory technicians: a new occupational disease? *J Allergy Clin Immunol* 1999;104:700–701.
- 6 Hartmann AL, Walter H, Wüthrich B: Occupational allergic asthma due to pectinase, a pectolytic enzyme. *Schweiz Med Wochenschr* 1983;113:265–267.
- 7 Weissenbach T, Wüthrich B, Weihe WH: Allergies to laboratory animals. An epidemiological, allergological study in persons exposed to laboratory animals. *Schweiz Med Wochenschr* 1988;118:930–938.
- 8 Bush R, Wood RA, Eggleston PA: Laboratory animal allergy. *J Allergy Clin Immunol* 1998; 102:99–112.
- 9 Global Initiative for Asthma: Global strategy for asthma management and prevention: NHLBI/WHO workshop report. Bethesda, National Institutes of Health, National Heart Lung and Blood Institute; 1998; NIH Publication No 96-3659B.

- ▶ 10 Prieto L, Sanchez-Toril F, Gutierrez V, Marin MJ: Airway responsiveness to inhaled acetaldehyde in subjects with allergic rhinitis: Relationship to methacholine responsiveness. *Respiration* 2002;69:129–135.
- ▶ 11 Cartier A, Malo JL, Pineau N, Dolovich J: Occupational asthma due to pepsin. *J Allergy Clin Immunol* 1984;73:574–577.
- ▶ 12 Tarvainen K, Kanera L, Tupeasela O, Grenquist-Nordén B, Jolanki R, Estlander T, et al: Allergy from cellulase and xylanase enzymes. *Clin Exp Allergy* 1991;21:609–615.
- ▶ 13 Bush RK: Assessment and treatment of laboratory animal allergy. *ILAR J* 2001;42:55–64.
- ▶ 14 Lieutier-Colas F, Meyer P, Pons F, Hedelin G, Larsson P, Malmberg P, Pauli G, De Blay F: Prevalence of symptoms, sensitisation to rats, and airborne exposure to major rat allergen (Rat n 1) and to endotoxin in rat-exposed workers: a cross-sectional study. *Clin Exp Allergy* 2002;32:1424–1429.
- ▶ 15 Platts-Mills TA, Longbottom J, Edwards J, Cockcroft A, Wilkins S: Occupational asthma and rhinitis related to laboratory rats: serum IgG and IgE antibodies to the rat urinary allergen. *J Allergy Clin Immunol* 1987;79:505–515.
- ▶ 16 Lushniak BD, Reh CM, Bernstein DI, Gallagher JS: Indirect assessment of 4,4'-diphenylmethane diisocyanate (MDI) exposure by evaluation of specific humoral immune responses to MDI conjugated to human serum albumin. *Am J Ind Med* 1998;33:471–477.
- ▶ 17 Bright P, Burge PS, O'Hickey SP, Gannon PF, Robertson AS, Boran A: Occupational asthma due to chrome and nickel electroplating. *Thorax* 1997;52:28–32.
- ▶ 18 Merget R, Sander I, Raulf-Heimsoth M, Baur X: Baker's asthma due to xylanase and cellulase without sensitization to alpha-amylase and only weak sensitisation to flour. *Int Arch Allergy Immunol* 2001;124:502–505.
- ▶ 19 Sarlo K, Ritz HL, Fletcher ER, Schrotel KR, Clark ED: Proteolytic detergent enzymes enhance the allergic antibody responses of guinea pigs to nonproteolytic detergent enzymes in a mixture: implications for occupational exposure. *J Allergy Clin Immunol* 1997;100:480–487.
- ▶ 20 Santaolalla M, De Barrio M, De Frutos C, Gandolfo M, Zuberdiá J, Rubio M, Rodríguez A, Baeza ML: Double sensitization to enzymes in a baker. *Allergy* 2002;57:957.
- ▶ 21 Lee SK, Cho HK, Cho SH, Kin SS, Nahm DH, Park HS: Occupational asthma and rhinitis caused by multiple herbal agents in a pharmacist. *Ann Allergy Asthma Immunol* 2001;86:469–474.