

CASE STUDY

Late asthmatic reaction with airway inflammation but without airway hyperresponsiveness

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Summary

We describe a subject who experienced a nonimmediate asthmatic reaction without airway hyperresponsiveness prior to the exposure or on repeated measurements, 90 min and 24 h after exposure. There was a major increase in sputum eosinophilia: 3% of cells obtained at baseline, 19% 90 min after exposure and 42% 24 h after exposure. We have demonstrated that a nonimmediate asthmatic reaction can occur without an increase in airway hyperresponsiveness despite a clear increase in eosinophilic airway inflammation.

Introduction

Airway hyperresponsiveness is a major characteristic of asthma and occupational asthma. It has been stated that the diagnosis of occupational asthma can be virtually excluded in patients with asthma-like symptoms if, after at least 2 weeks at work, their airway responsiveness remains normal [1]. Airway inflammation, another characteristic of asthma, has been found to be correlated with airway responsiveness in some instances [2]. We report the case of a patient with occupational asthma due to diacrylates proved by specific inhalation challenge, who experienced a nonimmediate asthmatic reaction after exposure to diacrylates, without increased airway responsiveness despite increased eosinophilic airway inflammation.

Case report

A 45-year-old man was employed for 1.5 years in a coach-building company. His job, painting trucks and cars, required using a primer containing diacrylates. Three months after the start of employment, he noticed symptoms of runny, stuffy nose and sneezing when at work. A few

weeks later, he noticed respiratory symptoms of shortness of breath, chest tightness, wheezing and persistent dry cough. These symptoms did not improve noticeably during weekends. When he stopped working for 2 months because of hand surgery, he became asymptomatic. He transferred to another company doing the same job, and 1 month later the same symptoms recurred. He stopped working in August 1997 because of his respiratory symptoms and became asymptomatic again. He was seen at our clinic in November 1997. He had been completely free from exposure from August to November. He had no previous personal or familial history of atopy and gave a smoking history of 18 pack-years, having quit 11 years earlier. He used no medication. Physical examination was normal. Skin prick tests to 22 common inhaled allergens were all negative.

Specific inhalation challenges were performed in November 1997 as previously described [3]. On a control day, baseline forced expiratory volume in 1 s (FEV₁) was 3.25 L (104% predicted) with a forced vital capacity (FVC) of 4.0 L (106% predicted). The patient was exposed to a paint thinner (commercial mixture of polyols) nebulized for a total of 30 min. The FEV₁ remained stable throughout the day. The airway responsiveness, measured at the end of the day using a standard procedure [4] was normal. PC₂₀ methacholine was 48 mg/mL. Next, the patient was exposed progressively to nebulized diacrylate in a provocation chamber for 4, 30 and 120 min, respectively, on 3 consecutive days. After the 120-min exposure, the patient experienced a nonimmediate asthmatic reaction starting 3 h after the end of the exposure with a maximum fall in FEV₁ of 23.7%. The PC₂₀ measured at the end of the day was 24 mg/mL, which does not represent a significant change according to the reproducibility of the test in our laboratory [5]. As airway responsiveness may at times be greater prior to a late asthmatic reaction than after 24 h [6], we thought that we might have missed an increase in airway responsiveness which had occurred before the late asthmatic reaction. We therefore decided to re-expose the subject 2 months later for 120 min to diacrylates and to carry out a methacholine

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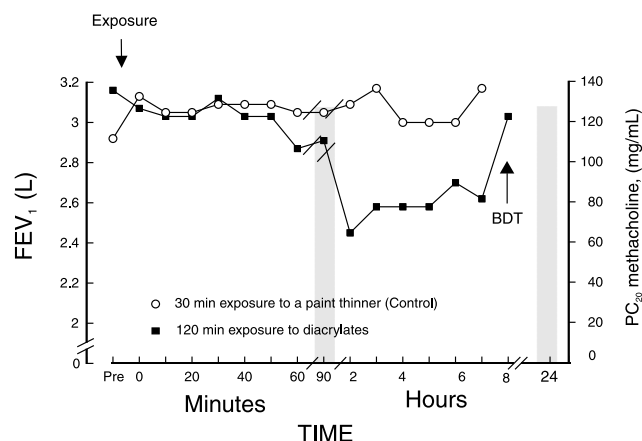


Fig. 1. Specific inhalation challenge to diacrylates showing a nonimmediate asthmatic reaction, grey bars represent PC_{20} values at the time of the challenge

challenge and a sputum induction [7] the day before, and at 90 min (before the late asthmatic reaction) and 24 h after the exposure.

The patient again experienced a nonimmediate asthmatic reaction beginning 2 h after the end of the exposure with a maximum fall in FEV_1 of 22.5%. Seven hours after the exposure, FEV_1 was still 17% lower than baseline. There was complete reversibility after the patient took bronchodilators (Fig. 1). Total cell count and percent of sputum eosinophils were significantly increased 90 min and 24 h after the exposure as compared with baseline values whereas there was again no change in airway responsiveness which remained within the normal range ($PC_{20} > 128$ mg/mL) (Table 1).

Discussion

Our results identify the occurrence of a nonimmediate asthmatic reaction without airway hyperresponsiveness but with airway inflammation. It is very unlikely that this lack of airway hyperresponsiveness is due to a false negative methacholine test since several subjects tested with the same methacholine batch on the same days as our subject had severe to mild airway hyperresponsiveness.

The occurrence of an asthmatic reaction without airway responsiveness, although previously described in some cases [8,9], is an unusual phenomenon. In most cases where the PC_{20} is normal before exposure, there is a significant decrease of the PC_{20} into the asthmatic range following a late asthmatic reaction [9]. Similarly to the case described by Banks *et al.* our subject showed a normal PC_{20} before and after a late asthmatic reaction [8]. However, there was no assessment of airway inflammation in that case.

Table 1. Characteristics of the subject in relation to exposure to the occupational sensitizer: diacrylates

	Normal values	Control	90 min after exposure	24 h after exposure
FEV_1 , L (% pred.)	3.1	3.0 (96)	2.74 (88)	2.74 (88)
PC_{20} (mg/mL)	> 16	> 128	> 128	> 128
<i>Induced sputum</i>				
TCC (10^6 /mL)	< 4.5	8.1	13.2	20.9
Eosinophils (%)	< 2	3	19	42
Neutrophils (%)	< 35	45	54	29

TCC – total cell count, PC_{20} – provocation concentration of methacholine to cause a fall in FEV_1 of 20%.

As this worker was seen 3 months after he had left work and as his employer did not allow him to return to work, we could not perform monitoring of peak-expiratory flow and airway responsiveness at work. We can speculate that he may have shown increased airway responsiveness at that time. A normal PC_{20} does not rule out the diagnosis of occupational asthma if the subject has been removed from the workplace for a while. The occurrence of a late asthmatic reaction in spite of normal airway responsiveness is difficult to predict since it is a rare phenomenon and has seldom been described in the literature. There is no predictive factor for the occurrence of such a reaction to our knowledge. Such reactions are expected to occur more often with low-molecular weight agents since nonimmediate asthmatic reactions are more frequent with these types of agents. However, there is no evidence that the occurrence of a late asthmatic reaction without airway hyperresponsiveness is due to the agent itself, diacrylates, as the previous cases reported were related to isocyanate exposure [8,9].

The relationship between the level of airway responsiveness and the magnitude of airway inflammation is controversial. Although several studies have described an association between airway responsiveness and airway inflammation as measured by percentage of mast cells and eosinophils [2], the relationship appears neither close nor straightforward [10]. Although our subject had a substantial increase in his sputum eosinophils (42%), no increase in airway responsiveness could be detected, suggesting that the occurrence of airway responsiveness is unlikely to be induced by airway inflammation alone. Airway responsiveness is probably induced by multifactorial parameters like airway inflammation, airway remodelling or airway smooth muscle dysfunction. Airway inflammation without asthma nor airway hyperresponsiveness has been described in subjects with chronic cough. This condition has been labelled as eosinophilic bronchitis [11]. It is possible that

in subjects with very low baseline responsiveness, a great deal of inflammation is necessary to induce airway responsiveness. It could also be hypothesized that in spite of the presence of eosinophils in the airways, these cells could have an altered behaviour without leading to airway responsiveness.

A significant inverse relationship between eosinophilic inflammation and baseline FEV₁ has been previously shown [10]. In our case, the occurrence of a late asthmatic reaction might be related to the presence of a major airway inflammation in spite of normal airway responsiveness. This case report further confirms that the three features of the asthmatic phenotype – airway obstruction, airway hyperresponsiveness and airway inflammation – need to be assessed as stated by Haley and Drazen [12].

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References

- Bernstein D. Clinical assessment and management of occupational asthma. In: *Asthma in the Workplace*; Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. New York, NY: Marcel Dekker, 1993:103–23.
- Wardlaw A, Dunnette S, Gleich G et al. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma. *Am Rev Respir Dis* 1988; 137:62–9.
- Cartier A. Definition and diagnosis of occupational asthma. *Eur Respir J* 1994; 7:153–60.
- Cockcroft D, Killian D, Mellon J et al. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; 7:235–43.
- Dehaut P, Rachiele A, Martin R et al. Histamine dose–response curves in asthma: reproducibility and sensitivity of different indices to assess response. *Thorax* 1983; 38:516–22.
- Durham S, Graneek B, Hawkins R et al. The temporal relationship between increases in airway responsiveness to histamine and late asthmatic responses induced by occupational agents. *J Allergy Clin Immunol* 1987; 79:398–406.
- Pizzichini E, Pizzichini M, Efthimiadis A et al. Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am J Respir Crit Care Med* 1996; 154:308–17.
- Banks D, Butcher B, Hammad Y et al. Absence of hyperresponsiveness to methacholine in a worker with methylene diphenyl diisocyanate (MDI)-induced asthma. *Chest* 1986; 89:389–93.
- Mapp C, Vecchio LD, Boschetto P et al. Toluene diisocyanate-induced asthma without airway hyperresponsiveness. *Eur J Respir Dis* 1986; 68:89–95.
- Crimi E, Spanevello A, Neri M et al. Dissociation between airway inflammation and airway hyperresponsiveness in allergic asthma. *Am J Respir Crit Care Med* 1998; 157:4–9.
- Gibson P, Dolovich J, Denburg J, Ramsdale E. Chronic cough: Eosinophilic bronchitis without asthma. *Lancet* 1989; 1(8651):1346–8.
- Haley KJ, Drazen JM. Inflammation and airway function in asthma: What you see is not necessarily what you get. *Am J Respir Crit Care Med* 1998; 157:1–3.