

CASE REPORT

Occupational eosinophilic bronchitis in a foundry worker exposed to isocyanate and a baker exposed to flour

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Eosinophilic bronchitis without asthma may occur as a consequence of occupational exposure. The cases of a foundry worker and a baker who developed symptoms, respectively, due to exposure to isocyanate and flour, are reported. Cough was not associated with variable airflow obstruction or with airway hyper-responsiveness and was responsive to inhaled corticosteroids. The eosinophilia detectable in their sputum was causally related to the occupational exposure in the workplace. The examination of induced sputum should be used in addition to the objective monitoring of lung function for workers who have asthma-like symptoms in an occupational setting.

Eosinophilic bronchitis is a condition which presents with chronic cough and is characterised by sputum eosinophilia (>3% of non-squamous epithelial cells) but, unlike asthma, there is no evidence of variable airflow obstruction and airway hyper-responsiveness.^{1,2} Exposure to certain occupational allergens or sensitisers, such as natural rubber latex,³ acrylates,⁴ mushroom spores⁵ and an epoxy resin hardener,⁶ have been reported to cause eosinophilic bronchitis without asthma. We report the cases of a foundry worker and a baker who developed chronic cough as a consequence of occupational exposure to isocyanate and flour, respectively.

CASE REPORT 1

A 44-year-old man had worked in a foundry for 8 years. He used to smoke 10 cigarettes daily and had no history of atopy and asthma. He described his job as making cores and, from the safety data sheet he gave us, it was apparent that he was exposed to methylene diphenyl isocyanate (MDI). He had never had respiratory symptoms before the previous 6 months, when he started having a non-productive chronic cough without wheezing or dyspnoea. The cough worsened at work and improved on weekends off work or holidays. Physical examination, chest radiography and peripheral blood count were normal. Table 1 shows the skin and blood tests for allergy, lung function and cellularity of sputum induced after the work shift. Sputum induction was performed as described by Pin *et al*⁷ within 6 h of the last exposure at work, and the sample was examined as described by Pavord *et al*.⁸ Owing to his cough, the worker was relocated by the foundry occupational physician to a new job in the foundry stores where he was not exposed to isocyanate. His cough improved, and after a month he was completely asymptomatic. Sputum induction was performed while asymptomatic and after specific bronchial challenge with isocyanate. Specific inhalation challenge with MDI was carried out in a 10 m³ dynamic chamber. An MDI atmosphere was generated in the chamber by passing dry air through MDI contained in a flask and injected into the ultrafiltered air stream in the chamber through a Venturi effect. The isocyanate concentration was continuously monitored with an MDA device (Iso-Check, SKC Instruments, Houston, USA). On the

day of the challenge, he was exposed to MDI up to a maximum concentration of 20 ppm for 30 min. After the isocyanate challenge, a non-productive persistent cough started, but no changes in forced expiratory volume in 1 s (FEV₁) occurred during the 24 h observation period. After this period, sputum induction was performed before the methacholine challenge. The methacholine challenge was normal at a maximal dose-response curve (provocative dose inducing a 20% fall in FEV₁ >3200 µg). Table 1 shows the percentages of non-squamous epithelial cells in induced sputum.

CASE REPORT 2

A 41-year-old male baker, non-smoker, had been exposed to flour for 10 years. In the previous 2 years he had developed a non-productive chronic cough without wheezing or dyspnoea. The cough worsened at work and waned during holidays. He was prescribed antitussive medication by his general practitioner, with a poor response, and was not receiving any medication for asthma. Physical examination and a chest radiograph (prescribed by the general practitioner 2 months before) were normal. Peripheral blood count was normal. Table 2 shows the skin and blood tests for allergy, lung function and cellularity of sputum induced after the work shift. Sputum induction as described by Pin *et al*⁷ was performed in the morning after his night shift, and the sample was processed as described by Pavord *et al*.⁸ As he occasionally had headache and heartburn, we also performed sinus radiography as well as 24-h gastric pH monitoring which were normal, excluding post-nasal drip and atypical symptoms of gastro-oesophageal reflux. He continued to work in the family bakery and treatment with inhaled fluticasone (500 µg daily) was started. He had a marked response to treatment and was asymptomatic after 1 month. While still receiving treatment and being followed up in our outpatient clinic, he took temporary leave from the bakery work so we discontinued his treatment and advised him to contact us if symptoms occurred and to come to our outpatient clinic before he started baking again. During this period he remained asymptomatic. Sputum induction was performed while asymptomatic, still exposed at work but taking inhaled steroids, and while asymptomatic, not exposed at work and after flour-specific bronchial challenge.

The flour bronchial challenge was performed, according to the European Respiratory Society guidelines⁹ in a worksite simulation with the patient's own flour samples. The patient shook approximately 100 g of flour in an open bag for up to 30 min, with flour concentrations in air (measured by nephelometry, Grimm Technik GmbH & Co. KG, Airing, Germany) ranging between 90 and 130 mg/m³. During the challenge he had a non-productive cough which persisted for several hours, but no changes in FEV₁ were measured during the 24 h observation period. After this period, sputum

Abbreviations: FEV₁, forced expiratory volume in 1 s; MDI, methylene diphenyl isocyanate

Table 1 Skin and blood tests for allergy, lung function and induced sputum of case 1

Skin prick test			
Common aeroallergens (Alk)*		Negative	
Total serum IgE		Normal (10 kU/l)	
Specific serum IgE (ImmunoCAP Pharmacia)	HDI	Negative (<0.35 kU _A /l)	
	MDI	Negative (<0.35 kU _A /l)	
	TDI	Negative (<0.35 kU _A /l)	
FEV ₁	3.14 litres (92% predicted value)		
FVC	4.1 litres (93% predicted value)		
FEV ₁ /FVC	75%		
Peak expiratory flow rate†	Daily variability <20%		
PD ₂₀ ‡	>3200 µg		
Induced sputum			
Total cell count (×10 ⁶ /ml)	After the work shift	While asymptomatic (not exposed at work)	After isocyanate bronchial challenge
	2.7	1.3	3.8
Non-squamous epithelial cells (%)			
Neutrophils	38	35	25
Eosinophils	35	0	60
Macrophages	27	65	15

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HDI, hexamethylene diisocyanate; MDI, methylene diphenyl isocyanate; PD₂₀, provocative dose inducing a 20% fall in FEV₁; TDI, toluene diisocyanate.

*House dust mites, pollens, cat and dog dander, moulds such as *Alternaria alternata*, *Aspergillus fumigatus* and *Cladosporium herbarum*.

†Peak expiratory flows measured six times daily for 4 weeks without significant changes at work or away from work.

‡Methacholine challenge performed soon after the work shift (approximately 3 h after) at a maximal dose-response curve.

Alk-Abellø, Horsholm, Denmark; ImmunoCAP Pharmacia, Uppsala, Sweden.

induction was performed before methacholine challenge. The methacholine challenge was normal at a maximal dose-response curve (provocative dose inducing a 20% fall in FEV₁ >3200 µg). Table 2 shows the percentages of non-squamous epithelial cells in induced sputum.

DISCUSSION

Occupational exposure to isocyanate and flour was the cause of eosinophilic bronchitis in cases 1 and 2, respectively. The condition was characterised by work-related changes in sputum eosinophils that were significant and reproducible. Causative

Table 2 Skin and blood tests for allergy, lung function and induced sputum of case 2

Skin prick test				
Common aeroallergens (Alk)*		Negative		
Baking allergens (Alk)				
Wheat flour		Positive†		
Rye flour		Negative		
Oat flour		Negative		
Corn flour		Negative		
Soy flour		Negative		
Total IgE		Increased (190 kU/l)		
Specific serum IgE (ImmunoCAP Pharmacia)	Wheat	Positive (16 kU _A /l)		
	α-Amylase	Negative (<0.35 kU _A /l)		
FEV ₁	3.49 litres (106% predicted value)			
FVC	4.62 litres (110% predicted value)			
FEV ₁ /FVC	78%			
Peak expiratory flow rate‡	Daily variability <20%			
PD ₂₀ §	>3200 µg			
Induced sputum				
Total cell count (×10 ⁶ /ml)	After the work shift	While asymptomatic (still exposed at work but taking inhaled steroids)	While asymptomatic (not exposed at work)	After flour bronchial challenge
	1.0	0.4	0.6	2.3
Non-squamous epithelial cells (%)				
Neutrophils	8	6	5	4
Eosinophils	40	2	0	54
Macrophages	52	92	95	42

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PD₂₀, provocative dose inducing a 20% fall in FEV₁.

*House dust mites, pollens, cat and dog dander, moulds such as *Alternaria alternata*, *Aspergillus fumigatus* and *Cladosporium herbarum*.

†Skin prick test positivity: a weal diameter of 5 mm, more than one half of that of the histamine control.

‡Peak expiratory flows measured six times daily for 4 weeks without significant changes at work or away from work.

§Methacholine challenge performed soon after the work shift (in the morning after the night shift) at a maximal dose-response curve.

agents of eosinophilic bronchitis in the workplace have rarely been established. To date, eosinophil bronchitis has been causally related to occupational agents only in the two patients described here and in two other published case reports.^{3,4} Challenge exposure to latex gloves in a nurse³ and acrylates in a worker⁴ resulted in a marked increase in sputum eosinophilia in the absence of airflow obstruction and bronchial hyper-responsiveness. In a cross-sectional health survey conducted on a mushroom farm,⁵ eosinophilic bronchitis was among the causes of chronic cough but a causal relationship between exposure to a specific occupational agent and sputum eosinophilia was not reproducibly demonstrated with specific occupational bronchial challenge.

It is not known why these patients do not have airway hyper-responsiveness despite the eosinophilic bronchial inflammation, nor whether they will progress to typical occupational asthma. A recent prospective follow-up study of patients with eosinophilic bronchitis not related to occupational exposure showed that recurrence of the disease, after an initial remission obtained with inhaled corticosteroids, was associated in some cases with the development of asthma or chronic airflow obstruction.¹⁰ Several hypotheses have been proposed to explain the eosinophilic bronchitis inflammatory response which does not cause bronchial hyper-responsiveness.¹¹ To examine the missing link between airway inflammation and airway hyper-responsiveness, the intricate relationships between inflammatory cells (eosinophils, lymphocytes, neutrophils), resident cells (mast cells, epithelial cells, macrophages), inflammatory mediators, cytokines and neuropeptides (substance P, neurokinin A, calcitonin gene-related peptide) secreted by the bronchial sensory nerves and bronchial smooth muscle cells need to be sustained. Although eosinophilic bronchitis does not meet the current definition of asthma, it should be regarded as an occupationally induced condition when work-related changes in sputum eosinophils are significant and reproducible. The examination of induced sputum should be part of the diagnostic algorithm for workers who have asthma-like symptoms in an occupational setting. It is a further diagnostic tool which complements the objective monitoring of lung function during periods at work and away from work, as well as

before and after specific bronchial challenges with occupational agents.

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