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BRIEF COMMUNICATION

Occupational exposure to toluene diisocyanate and neutrophilic bronchitis without asthma

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Context. Isocyanates represent a leading cause of occupational asthma, and sputum neutrophilia or eosinophilia has been described in subjects with isocyanate-induced occupational asthma after exposure to these chemicals. One case of non-asthmatic eosinophilic bronchitis due to methylene diphenyl isocyanates has been reported, but a similar condition in the instance of neutrophilic bronchial inflammation has never been described. **Case details.** We report a 34-year-old woman, who, 18 months after beginning work in a plastic industry, reported the onset of dry cough at work. Spirometry was normal, reversibility and methacholine challenge tests were negative. A specific inhalation challenge with toluene diisocyanate elicited dry cough without significant changes in respiratory function. Sputum induction showed a post-challenge neutrophil increase. **Discussion.** The results of our case suggest that the occurrence of a neutrophilic bronchial inflammation without the functional characteristics of occupational asthma as a consequence of exposure to toluene diisocyanate may also be considered, suggesting a diagnosis of occupational non-asthmatic neutrophilic bronchitis.

Keywords Lung; Occupational asthma; Isocyanate; Eosinophilic bronchitis; Occupational respiratory disease

Introduction

Isocyanates represent a leading cause of occupational asthma (OA).¹ Some authors have shown that exposure to these chemicals induces OA with sputum neutrophilia as the main inflammatory pattern,² whereas others have observed sputum eosinophilia.³ In 1989, a condition characterized by corticosteroid-responsive chronic cough, sputum eosinophilia, and absence of symptoms or objective evidence of variable airflow obstruction and airway hyper-responsiveness was recognized and labeled as non-asthmatic eosinophilic bronchitis (NAEB).⁴ Like asthma, NAEB can be associated with exposure to occupational sensitizers,⁵ and only one case due to methylene diphenyl isocyanates has been reported to date.⁶ A similar condition in the instance of neutrophilic bronchial inflammation has never been described. We report the first case of occupational non-asthmatic neutrophilic bronchitis due to toluene diisocyanate (TDI) exposure.

Case description

A 34-year-old female, ex-smoker (0.15 pack-years from the age of 17 to 18 years), came to our attention because of a work-related chronic cough. She started working as a clerk in a plastic industry at the age of 32; 18 months later, she reported

the onset of dry cough at work. Symptoms improved during weekends and holidays. Her office was situated in the manufacturing department and she was exposed to the chemicals present in this area. She reported of another employee suffering from work-related respiratory disorders. Safety sheets and risk assessment provided by the employer revealed the extensive use of TDI during the manufacturing process.

The patient was admitted to our hospital to investigate the work-relatedness of the reported symptoms, free of any therapy, and underwent the diagnostic pathway for OA. Spirometry was normal (FEV₁ 3.56 L-113% predicted), and reversibility and methacholine challenge tests (FEV₁ increase < 12% after administration of 400 mcg of salbutamol and PD₂₀FEV₁ > 1976 µg, respectively) were both negative. No sensitization to common allergens was found. Blood eosinophils were 0.9%, blood neutrophils 69.7%, and total serum IgE 13.9 kU/L (normal value < 120 kU/L).

A few days after the last work exposure, a specific inhalation challenge (SIC) was performed by controlled evaporation of 2 µL of pure TDI in a steel pot in an inhalation chamber (cumulative exposure: 240 min)⁷ and elicited dry cough 5 min after the end of exposure. The maximum FEV₁ fall (8%) was registered 15 min after the end of the exposure. A methacholine challenge test performed 24 h after the SIC was negative (PD₂₀FEV₁ > 1976 µg). No FEV₁ change or symptoms were registered on a control challenge with isobutylacetate, performed the day before the SIC.

Sputum induction (IS) was performed before and 24 h after exposure.^{8,9} IS showed a post-SIC neutrophil increase (from 3.9% [2.14 cells × 10⁴/mL] to 51.7% [38 cells × 10⁴/mL]), and no bronchial eosinophilia (0% both pre- and after-SIC).

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Most lymphocytes in IS were identified with flow cytometry as CD4 + both pre- (71.3% of CD3 + cells) and after the SIC (71.9% of CD3 + cells). After discharge, the patient was asked to stay off work for 2 weeks, free of any therapy. At the end of this period, the patient was asymptomatic. IS showed 8.5% ($4.4 \text{ cells} \times 10^4/\text{mL}$) neutrophils and 0% eosinophils. Other causes of chronic cough (e.g. gastroesophageal reflux disease) were ruled out and a diagnosis of non-asthmatic neutrophilic bronchitis (NANB) due to TDI was suggested.

To exclude a non-specific inflammatory response to TDI, data were compared with those of a 31-year-old non-atopic patient, referred to our unit because of a clinical history of respiratory symptoms related to TDI exposure, who underwent an SIC with the same method. The challenge was negative (maximum FEV₁ fall 1%), IS neutrophils were 13% pre- and 10.9% post-SIC, and eosinophils 2.9 and 2%, respectively, allowing to conclude that the experimental exposure to TDI was able to induce a neutrophil increase only in sensitized patients and not in all exposed workers.

Informed consent was obtained from the patient. No IRB approval was required as in our practice an SIC is commonly performed in patients with suspected occupational respiratory diseases in whom other diagnostic approaches have been inadequate and for those with mixed or unusual exposures.

Discussion

The airway inflammation induced by exposure to isocyanates is variable, but sputum neutrophilia has frequently been documented as the main inflammatory pattern.² As a consequence, as described for eosinophilic inflammation, the occurrence of a neutrophilic bronchial inflammation without the functional characteristics of OA should also be considered. In the present case, the onset of dry cough and the IS neutrophil increase after an SIC, and the low percentage of IS neutrophils when the patient was not exposed to TDI at work were consistent with a work-related disease. However, the diagnostic criteria for OA were not fulfilled.¹⁰

The neutrophil recruitment in the airways, together with the presence of CD8 T cells, has been described as secondary to respiratory infections. In our case, the absence of suggestive symptoms and the prevalence of sputum CD4 + T lymphocytes both pre- and post-SIC did not suggest a neutrophil recruitment secondary to a respiratory infection. Many factors (such as air pollution, endotoxin contamination of the environment, etc.) are reported to induce bronchial neutrophilia. In our case, the subject had a very low percentage of IS neutrophils when out of work and a significant increase when exposed to a specific workplace chemical (i.e. TDI). These remarks, along with the absence of inflammation in the control patient, and the exclusion of other causes of chronic cough (i.e. antihypertensive medication, active or passive smoke, gastroesophageal reflux) permitted us to exclude a non-specific response.

The use of reliable methods to measure inflammatory cells during an SIC has allowed the identification of new entities

in the spectrum of occupational respiratory disorders.¹¹ Thus, analogous to NAEB, it is possible that there is a similar condition characterized by work-related cough, neutrophilic inflammation in the absence of symptoms or objective evidence of variable airflow obstruction and airway hyper-responsiveness. It may be suspected when cough, occurring after exposure to occupational agents known to induce bronchial neutrophilic inflammation, is not associated with evidence of hyper-responsiveness or variable airflow limitation.

The possible outcome of this condition is unknown, but it is well known that continued exposure to an inflammatory agent like TDI might induce a chronic inflammation. Therefore, as suggested for NAEB, the possibility of developing a chronic airway obstruction may be taken into account. The correct identification of this condition could be important for taking preventive measures aimed at reducing the exposure to the offending agent and preventing possible subsequent diseases, like asthma and chronic obstructive pulmonary disease, due to exposure to airborne chemicals such as TDI.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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