

Case report

Reactive airways dysfunction syndrome induced by exposure to a mixture containing isocyanate: functional and histopathologic behaviour

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A 31-year-old machinist experienced acute symptoms of rhinoconjunctivitis, coughing, shortness of breath, and wheezing after sudden exposure to fumes containing isocyanates and solvents. Lung function tests carried out 11 days after the event showed reduced flow rates. Forty days after the acute inhalational injury, expiratory flows improved, and the PC_{20} was 0.8 mg/ml, showing moderate bronchial hyperresponsiveness. Six days later, the subject underwent bronchoscopy. Bronchial biopsies showed a marked loss of epithelial cells, severe subepithelial oedema, and inflammatory cells infiltrate (mainly lymphocytes). The subject was given inhaled steroids. The PC_{20} was back to normal 42 days later. Bronchial biopsies then showed incomplete regeneration of the epithelial layer with few ciliated cells and persistence of inflammation (lymphocyte infiltrate) in epithelia and connective tissue. We conclude that irritant exposure to a mixture of isocyanates and solvents can cause occupational asthma without a latency period, i.e., reactive airways dysfunction syndrome.

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Two types of occupational asthma can be distinguished by whether the disorder appears with or without a latency period (1). Reactive airways dysfunction syndrome (RADS) is a form of irritant-induced asthma which develops after a single exposure to an irritant material (2). Patients are left with "asthma-like symptoms" and airway hyper-responsiveness.

The time course and mechanisms of development of this entity are still to be defined. We describe a case of RADS in a subject who experienced irritant exposure to isocyanates and its diluents at the workplace. We obtained follow-up information derived from serial lung function tests and bronchial biopsy materials.

Case report

The 31-year old subject had been employed for 6 years as a machinist for a company in which he

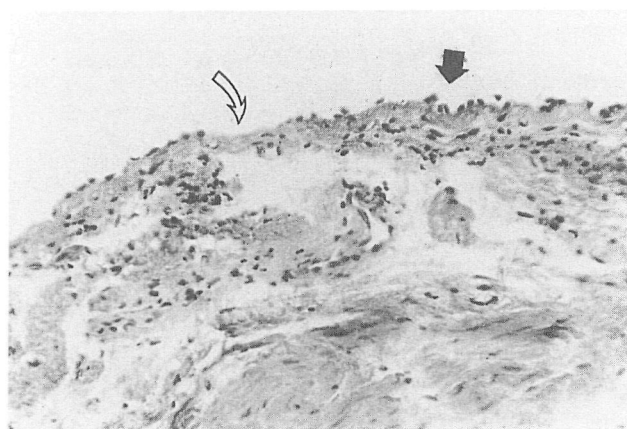
normally polished metal with oil. The workplace was located approximately 100 m from a large, well-ventilated paint shop in which isocyanates mixed with organic solvents (aliphatic polyisocyanates, hexamethylene diisocyanate, isophorone diisocyanate, aromatic hydrocarbon, ethyl acetate, propylene glycol, toluene, xylene, and tritolyl phosphate) were used for spray-painting. The subject never went into these paint shops. He had never experienced respiratory symptoms. He had stopped smoking 5 years before and had smoked 5 packs-years.

On 12 August 1994, a large piece of metal had to be painted outside the paint shop. By 1–2 h after the spraying started, several employees who were present started experiencing symptoms of runny eyes and nose, headache, and nausea. The subject also reported symptoms of cough, shortness of breath, and wheezing. He left after 3–4 h of exposure. On 23 August, he was seen by a chest physi-

cian, who noticed expiratory wheezing. Spirometry showed a reduced FEV₁ value of 2.9 l (pred [3]=5.41) (54% pred) and forced vital capacity (FVC) (3.6 l, pred [3] of 6.11 (59% pred). He took salbutamol on demand. He was assessed on 21 September. He still complained of dyspnoea, cough, and wheezing on exercise. Chest auscultation was normal. His FEV₁ was 4.6 l (84% pred) and his FVC, 4.9 l (81% pred). The provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) measured by a standardized procedure (4) (output of the nebulizer=0.14 ml/min) was 0.8 mg/ml (moderate hyperresponsiveness). Skin tests carried out by the prick method with 15 common inhalants were all negative. Bronchoscopy was performed on 27 September. Bronchial biopsies examined on light and electronic microscopy showed a severe loss of epithelial cells and marked subepithelial oedema with an inflammatory cell infiltrate underneath the basement membrane (Fig. 1). The number of inflammatory cells/mm² was obtained (5) and immunohistochemistry was carried out. This showed 43 cells/mm² of connective tissue surface, of which 26 were lymphocytes and nine, neutrophils. Immunohistochemistry staining showed most of the lymphocytes to be of CD45 and CD3 types. The subject was given inhaled steroids (beclomethasone, 2 mg daily). He was reassessed on 19 October. He had tried to resume work on 11 and 12 October but experienced symptoms of cough, dizziness, and wheezing which forced him to leave work. The subject then reported having been indirectly exposed to isocyanates at work. His PC₂₀ was 31 mg/ml, indicating no significant hyperresponsiveness. In order to exclude the possibility that high exposure to isocyanates had induced "sensitization" to isocyanates, we carried out specific inhalation challenges by exposing the subject to increasing concentrations of the mixture of isocyanates and solvents for not more than 2 h. These challenges failed to induce a significant fall in FEV₁. The subject was kept on high doses of inhaled beclomethasone (2 mg daily), and bronchoscopy was repeated on 17 November, when the PC₂₀ was 19 mg/ml (not significantly changed). This showed an incomplete regeneration of the epithelial layer with few ciliated cells. Inflammatory cells persisted in epithelia and connective tissue (Fig. 2) (188 cells/mm² of connective-tissue surface, 130 cells being lymphocytes, of which most were CD45 and CD3 types as revealed by immunohistochemistry).

Discussion

We herein report a case of RADS due to irritant exposure to isocyanates and its diluents. Even if it



(a)



(b)

Fig. 1. A) Light micrograph of bronchial biopsy 46 days after single massive exposure to isocyanates. Severe loss of epithelial cells (open arrow) with few remaining basal cells (shaded arrow). Subepithelial oedema with inflammatory cells (mainly lymphocytes) underneath basement membrane (hematoxylin-eosin [H-E] stain $\times 250$).

Fig. 1. B) Electron micrograph of first biopsy. Epithelial cell loss at luminal surface with fibrin deposition and intrafibrillar oedema (arrow). Epon-embedded material stained with uranyl acetate and lead citrate ($\times 2700$).

is not possible to be sure that isocyanates alone caused these symptoms, as there were various solvents mixed with the isocyanates, they were probably the offending agent. Fuchs & Valade have described cases of intoxication by isocyanates (6). However, it is difficult to distinguish between a toxic reaction and a "sensitization" reaction in these observations. This criticism also applies to the case reported by Boulet (7). Brugsch & Elkins (8) described symptoms experienced in 48 cases of intoxication by isocyanates. There was no functional or histologic evidence of RADS. Nevertheless, some of these subjects reported symptoms consistent with RADS after exposure to a spill of isocyanates. A few years later, Axford et al. (9) reported that most of a group of 35 firemen exposed to chemical fumes



(a)



(b)

Fig. 2. A) Light micrograph of second bronchial biopsy 98 days after isocyanate exposure. Incomplete regeneration of epithelial layer with few ciliated cells (arrows). Inflammatory cells (mainly lymphocytes) persist in epithelia and connective tissue (H-E stain $\times 250$).

Fig. 2. B) Electron micrograph of second biopsy. Epithelial cells with incomplete cilia genesis and dilatation of smooth endoplasmic reticulum. Lymphocytes at lower part of figure (arrow) (uranyl acetate and lead citrate staining, $\times 2700$).

including toluene diisocyanate (TDI) developed respiratory symptoms within 24 h of this single high exposure. Almost 4 years later, 20 subjects had persistent respiratory symptoms. More recently, Luo et al. (10) reported the case of two police officers who developed an asthma-like illness after a single exposure to TDI. Follow-up examination over 7 years showed persistence of respiratory symptoms and airway obstruction, but the authors did not describe the course of bronchial responsiveness. We herein report for the first time, to our knowledge, a case of RADS caused by isocyanates in which the course of bronchial responsiveness is described and results of bronchial biopsies are presented. Few authors (2, 11) have reported histopathologic changes among subjects suffering from RADS. Mild chronic inflammation and focal

desquamation of the epithelial layer, as well as bronchial wall thickening, are features of this condition. However, in these works, biopsies were taken at least 1 year after the single exposure to the offending agent. Our first biopsies were performed only 6 weeks after the exposure. Features of injury to the epithelial layer seemed more pronounced than those described in the previous observations (2, 11). The bronchial inflammatory infiltrate was less pronounced than what we recently reported in subjects with allergic rhinitis (5). Biopsies performed 3 months after exposure showed regeneration of the epithelial layer with less collagen deposition than what has been noticed approximately 1 year after an inhalational accident (11).

The time course of functional changes among subjects suffering from RADS is not yet well known. The effect of inhaled steroids on RADS is also unknown. The spirometric values of our subject improved 1 month after exposure without any treatment, but there was still moderate bronchial hyperresponsiveness. After a month and a half of inhaled steroid treatment, PC_{20} improved significantly toward normal values. Functional recovery could have been enhanced by inhaled steroids even though such improvement could represent the natural course that RADS would follow without treatment. Further studies of RADS need to be performed to evaluate the course of this disease from the functional and pathologic points of view, with and without anti-inflammatory treatment.

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References

- Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein D. Asthma in the workplace. New York: Marcel Dekker, 1993.
- Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest* 1985;88:376-84.
- Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127:725-34.
- Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7:235-43.
- Boulet LP, Turcotte H, Carrier G, Boutet M, Laviolette M. Increased maximal airway response to methacholine during seasonal allergic rhinitis in nonasthmatic subjects: relationships with airway wall thickness and inflammation. *Eur Respir J* 1995;8:913-21.

6. Fuchs S, Valade P. Étude clinique et expérimentale sur quelques cas d'intoxication par le Desmodur T (diisocyanate de toluylène 1-2-4 et 1-2-6). *Arch Mal Profess* 1951;12:191-6.
7. Boulet LP. Increases in airway responsiveness following acute exposure to respiratory irritants. Reactive airways dysfunction syndrome or occupational asthma? *Chest* 1988;94:476-81.
8. Brugsch HG, Elkins HB. Toluene di-isocyanate (TDI) toxicity. *N Engl J Med* 1963;268:353-7.
9. Axford AT, McKerrow CB, Jones AP, Lequesne PM. Accidental exposure to isocyanate fumes in a group of firemen. *Br J Ind Med* 1976;33:65-71.
10. Luo JC, Nelsen KG, Fischbein A. Persistent reactive airways dysfunction syndrome after exposure to toluene diisocyanate. *Br J Ind Med* 1990;47:239-41.
11. Gautrin D, Boulet LP, Boutet M, et al. Is reactive airways dysfunction syndrome (RADS) a variant of occupational asthma? *J Allergy Clin Immunol* 1994;93:12-22.

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