

CASE REPORT

Cutaneous sensitization to aziridine preceding the onset of occupational asthma

P. Mason,^{*} F. Liviero, M. Crivellaro, P. Maculan, P. Maestrelli and G. Guarnieri

Department of Cardiac-Thoracic-Vascular Sciences and Public Health, University of Padova, via Giustiniani 2, 35128 Padova, Italy.

Correspondence to: P. Maestrelli, Department of Cardiac-Thoracic-Vascular Sciences and Public Health, University of Padova, via Giustiniani 2, 35128 Padova, Italy. Tel: +390498212564; fax: +390498212566; e-mail: piero.maestrelli@unipd.it

Abstract We describe a 47-year-old non-atopic woman, working as a spray painter in a tannery for 23 years, with a 16-year history of cutaneous symptoms and a subsequent 2-year history of asthmatic symptoms after exposure to aerosol and vapour of polyfunctional aziridine (PFA) at work. To confirm the occupational origin of the dermatitis and asthma we performed a skin prick test with PFA and a specific inhalation challenge (SIC) with PFA. Prick test with PFA elicited an immediate positive skin reaction. She developed an immediate asthmatic reaction upon SIC with PFA. The onset of occupational dermatitis before asthma is consistent with the hypothesis that the sensitization to PFA was triggered in the skin. The observation that the reactions elicited in skin and airways upon exposure to PFA exhibited the same time course, suggests a similar mechanism at both sites. Thus, the avoidance of both skin and airway exposure to PFA should be recommended in workplace hygiene practice.

Key words Contact dermatitis; inhalation challenge; occupational asthma; skin test.

Background

Polyfunctional aziridine (PFA), Chemical Abstracts Service (CAS) no. 64265-57-2 [1], is a hardener used by tanners, spray painters, printers, photographers, etc. to strengthen the final products. It is known to have irritant and sensitizing properties for the skin and the airways. Few cases of dermatitis and occupational asthma (OA) due to PFA have so far been described and the mechanisms of sensitization are unknown [2–5]. We describe the case of a spray painter exposed to several chemical agents known to cause OA and contact dermatitis (e.g. formaldehyde; hexamethylene diisocyanate [HDI]; PFA), who exhibited dermatitis and asthmatic symptoms due to PFA. The occupational origin of the skin and respiratory disease was confirmed by performing a skin prick test and a specific inhalation challenge (SIC) with PFA.

Case presentation

A 47-year-old woman, who has worked as spray painter in a tannery for 23 years, was referred to our service by the company occupational physician. She complained of work-related cutaneous and respiratory symptoms only when she used PFA.

PFA was sometimes used as a cross-linker in polyurethane paints to make the leather more resistant to abrasion, solvents or moisture [6]. Her duties included preparing the varnishes by mixing products containing PFA and HDI and spray painting the leather. She wore rubber gloves intermittently, but no respiratory protective equipment was supplied. She also stated that the working area did not have exhaust ventilation systems.

The patient was evaluated according to the clinical history and the information retrieved from the safety data sheets of the chemical products that she used. Baseline lung function tests (including fractional exhaled nitric oxide [FeNO] measurements and induced sputum collection), skin prick tests with common aeroallergens, PFA, SIC with PFA and HDI were performed. The sham exposure and SIC with PFA were performed single blind as previously described [2]. The patient painted 30 mL of PFA or water on to a plate with a surface of 400 cm² in a 9-m³ challenge chamber. The scheduled test time was 60 min both for the sham and active exposures. We monitored lung function and FeNO concentrations for 7 h after sham and SIC. Sputum was induced and collected at baseline and 24 h post-SIC. SIC with HDI was performed 3 weeks after SIC with PFA, as previously described [7].

Key learning points

What is already known about this subject:

- Polyfunctional aziridine is a hardener known to have irritant and sensitizing properties for the skin and the airways.

What this study adds:

- Our case report suggests that the skin was the trigger for the occupational sensitization to polyfunctional aziridine and for the development of both cutaneous and respiratory symptoms.

What impact this may have on practice or policy:

- The polyfunctional aziridine data sheets recommended that employees engaged in handling polyfunctional aziridine must be provided with eye shields, gloves and a respirator. Adherence to these recommendations should be mandatory.

The patient denied any personal or familial allergic or respiratory diseases and had never smoked. She reported the onset of cutaneous lesions after 7 years of exposure to PFA, described as face, hands, and arms erythematous, itchy, dry rash, that improved when she was not exposed to PFA at work, but took >1 week to disappear. She also exhibited a subsequent 2-year history of work-related asthma symptoms (chest tightness, diurnal and nocturnal cough), which completely recovered after a few weeks on vacation. These symptoms occurred approximately once a month, when PFA was used and were preceded by mild symptoms of rhinoconjunctivitis in the workplace. At the time of our evaluation, when she had been removed from her workplace for 9 months, respiratory symptoms had recovered. Her skin was nearly normal, apart from the facial and hands sequelae of previous lesions. Chest examination was normal. Baseline lung function tests were normal (vital capacity [VC], % of predicted: 94; forced expiratory volume in 1 s [FEV₁], % of predicted: 95; FEV₁/VC ratio: 0.75; FeNO: 21 ppb). Peripheral blood eosinophils count was normal ($0.07 \times 10^9/L$). The analysis of the induced sputum at baseline showed: 2.4% eosinophils, 10.3% neutrophils and 81.8% macrophages. Skin prick tests with common aeroallergens and latex were negative. The skin tests were performed also with dilutions of the PFA hardener and we obtained positive results at different concentrations from 1/1 to 1/100 (Figure 1a). SIC with PFA was positive since the patient developed an acute asthmatic reaction after 25 min of exposure to PFA, with a fall in FEV₁ of 21% compared to baseline values, whereas no changes in FEV₁ were observed after sham (Figure 1b). No dermatitis appeared upon SIC with PFA. FeNO values remained stable over the 24 h post-SIC (Figure 1c), whereas a substantial increase of neutrophils (40.5%), but not of eosinophils, was detected in induced sputum at 24 h after SIC (Figure 1d). The subsequent SIC with HDI was negative.

At follow-up visits (performed at 1 and 11 months post-SICs) the patient had been removed from the

exposure to PFA. She was asymptomatic, and clinical examination and lung function were normal.

We describe a new rare case of asthma due to PFA, in which cutaneous sensitization preceded the onset of OA of several years. To confirm the occupational origin of the respiratory disease, we relied on a positive SIC and we were also able to characterize the airway inflammation by FeNO and induced sputum.

FeNO is considered an eosinophilic marker of the airways and in previous studies, we demonstrated that it shows a delayed increase 24 h after SIC in subjects sensitized to low molecular weight (LMW) agents such as diisocyanates. FeNO increase was due to changes in NO dynamics within the airways and associated with eosinophilia in induced sputum [7, 8]. In this patient, there was no evidence of eosinophilia induced by PFA exposure. In contrast, the increase in airway neutrophils upon SIC suggests that the mechanism underlying asthma induced by PFA is different from that of other LMW chemicals such as diisocyanates.

The dermatitis due to PFA resembled the 'protein contact dermatitis' entity [9], since the skin lesions persisted for longer than those of a simple urticaria after cessation of work exposure. The pathogenesis of protein contact dermatitis is unclear, but it generally involves an immediate hypersensitivity reaction, often Immunoglobulin E-mediated, as described in a recent review by Barbaud *et al.* [10]. There is a growing interest in determining whether skin exposure to occupational agents can lead to respiratory sensitization and/or elicit airway reactions [11]. Studies in naïve animals exposed via skin to different LMW agents in order to induce sensitization demonstrated that the animals developed asthma-like response upon subsequent respiratory exposures (e.g. toluene diisocyanate, methylene diphenyl diisocyanate, trimellitic anhydride) [12, 13]. In humans, there are case reports describing the concomitant occurrence of allergic occupational contact dermatitis and OA, but few epidemiological studies estimated the incidence of workers reporting both skin and respiratory work-related symptoms [14, 15].

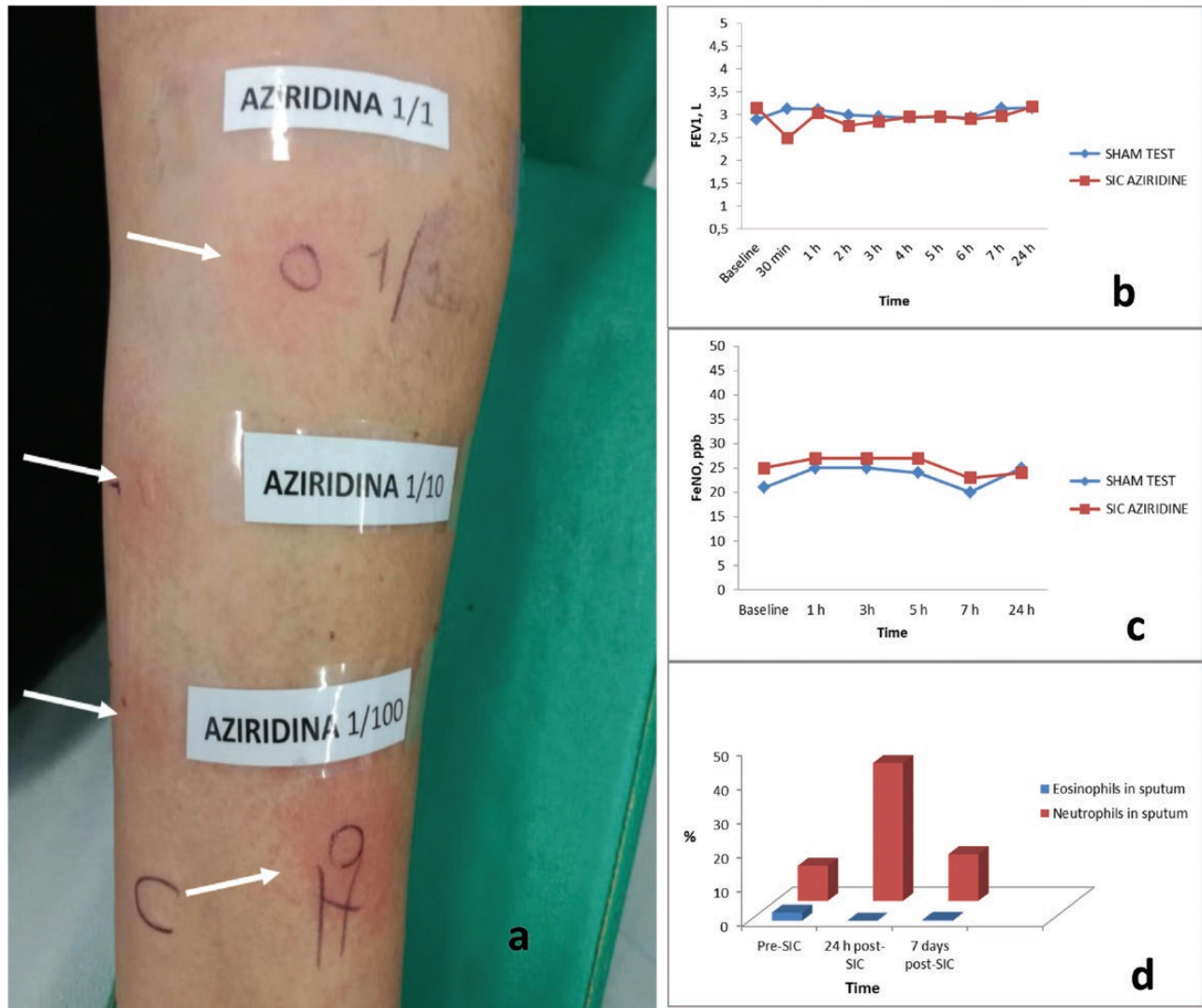


Figure 1. (a) Results of prick by prick skin test with PFA; arrows indicate the areas of the skin reactions elicited by the different concentrations of PFA (“aziridina” in Italian) and by histamine, as positive control (C H); pen marks within the erythematous lesions denote the wheal area. (b) FEV₁ changes during sham and SIC with PFA; (c) FeNO changes during sham and SIC with PFA; (d) percentages of eosinophils and neutrophils in induced sputum pre- and post-SIC with PFA.

In our patient, a simultaneous exposure of skin and airways occurred by PFA aerosol, since she did not use individual protective equipment apart rubber gloves, worn intermittently. The cutaneous sensitization preceding respiratory symptoms suggests that skin exposure was also able to induce respiratory sensitization. In addition, the same time course of the hypersensitivity reactions elicited by skin and airway exposure to PFA suggests the hypothesis that the mechanisms underlying skin and lung sensitization to PFA might be similar at both sites. Helaskoski *et al.* [14] retrospectively reviewed the cases of contact urticaria or protein contact dermatitis and concomitant airway diseases. They obtained data on 291 cases of occupational skin diseases and 46% of subjects had a concomitant airway disease caused by the same work-related chemical. A total of 60 patients

were diagnosed with concomitant OA (21%) and 111 patients were diagnosed with occupational rhinitis (38%) caused by the same agent that triggered the cutaneous disease. The skin symptoms appeared before the respiratory symptoms in 37 cases, while in 26 cases the respiratory symptoms appeared first. In a study by Merget *et al.* [15] among 96 workers with OA induced by platinum salts, 53% of participants also had skin complaints detected from self-administered questionnaire.

Preventive measures against sensitizers in the workplace are generally focused on protecting the respiratory tract presuming that it is the key route of exposure and the site for initiation of the immune response. However, we have provided evidence that it should be mandatory to avoid both skin and airway exposure to PFA, or to similar volatile sensitizing compounds, by adopting

technical interventions in the workplace (e.g. replacement of the chemical or automation of the tasks) and to promote the regular use of appropriate personal protective equipment.

Competing interests

None declared.

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