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CASE REPORT

Acute life-threatening extrinsic allergic alveolitis in a paint controller

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Background Occupational diisocyanate-induced extrinsic allergic alveolitis (EAA) is a rare and probably underestimated diagnosis. Two acute occupational EAA cases have been described in this context, but neither of them concerned hexamethylene diisocyanate (HDI) exposure.

Aims To investigate the cause of a life-threatening EAA arising at work in a healthy 30-year-old female paint quality controller.

Methods Occupational medical assessment, workplace evaluation, airborne and biological monitoring and immunodermatological tests.

Results Diagnosis of EAA relied on congruent clinical and radiological information, confirmed occupational HDI exposure and positive IgG antibodies and patch tests. The patient worked in a small laboratory for 7 years, only occasionally using HDI-containing hardeners. While working with HDI for 6 h, she developed breathlessness, rapidly progressing to severe respiratory failure. Workplace HDI airborne exposure values ranged from undetectable levels to 4.25 p.p.b. Biological monitoring of urinary hexamethylene diamine in co-workers ranged from <1.0 to 15.4 μg/g creatinine. Patch tests 8 months later showed delayed skin reaction to HDI at 48 h. Subsequent skin biopsy showed spongiotic dermatitis with infiltration of $CD4^+$ and $CD8^+$ T cells.

Conclusions We believe this is the first reported case of acute life-threatening EAA following exposure to HDI. Low concentrations of airborne HDI and relatively high urinary hexamethylene diamine suggest significant skin absorption of HDI could have significantly contributed to the development of this acute occupational EAA.

Key words Hexamethylene diisocyanate; occupational extrinsic allergic alveolitis (EAA); occupational hypersensitivity pneumonitis; paint quality control.

Introduction

As haptens, isocyanates can induce different humoral (IgE and IgG) and cellular (T-cell) immune mechanisms. Clinically, these reactions can cause allergic asthma and extrinsic allergic alveolitis (EAA) or hypersensitivity pneumonitis, presumably through both type-III and type-IV immunity [1].

Few cases of isocyanate-induced occupational EAA have been reported [2–5], and most are subacute or chronic forms, affecting workers in car body repair shops [2, 3, 5] or polyurethane foam production [4].

Inhalation is considered the main route for isocyanate exposure. However, human and animal studies suggest respiratory sensitization and disease exacerbation from dermal exposure [6].

We describe possibly the first reported case of acute life-threatening occupational EAA related to hexamethylene diisocyanate (HDI) exposure.

Case report

In June 2008, a 30-year-old healthy female paint quality controller (5 pack/years smoker) developed breathlessness, cough, chest tightness, malaise, sweating and chills in her workplace. Severe respiratory failure (PaO_2 5.6 kPa, $PaCO_2$ 4.4 kPa) and hemoptysis followed rapidly. Examination revealed left basal and right mid-lung crackles, respiratory rate of 24/min and temperature 37.6°C.

Blood test findings included raised C-reactive protein (11 mg/l), thrombocytopenia (71 G/l), raised liver enzymes

(aspartate aminotransferase 124; alanine aminotransferase 140 U/l) but normal white cell count (5.8 G/l). Infection and autoimmune and toxicology screening were negative.

Chest radiography showed diffuse bilateral infiltrates and ground-glass appearance on high-resolution computerized tomography, mainly in the basal lung fields, with thickened interlobular septa on both apical sides (Figure 1).

Two hours after admission, sudden respiratory worsening was treated with high concentration oxygen and systemic corticosteroids in the intensive care unit, with rapid improvement. Oxygen was stopped at Day 3 and radiographic abnormalities almost resolved by Day 5.

In September 2008, we performed a workplace investigation. The patient worked as a paint quality controller for 7 years, mixing small specimens of acrylic paints. For up to six non-consecutive weeks per year, she also dealt with HDI-based hardeners in the same way. She used short latex gloves but no respiratory protection or lab coat. On the day of the acute event, she had been using an HDI-containing hardener (70–80% HDI-based aliphatic polyisocyanate and 0.1–0.5% hexamethylene-1, 6-diisocyanate monomers) for 6 h when the first symptom occurred.

In the laboratory, only two employees work as paint controllers in a separate room. Neither the second paint controller nor the 10 coworkers reported any respiratory symptoms. Air renewal rate was 1.5 times/h. To avoid potential toxic isocyanate exposure, this should be at least 10 times higher. We measured HDI-air exposure and collected urine samples from two other paint controllers, after a 45-min work session using the same paints as on the day of the incident. Stationary HDI air exposure values ranged from undetectable to 4.25 p.p.b. Personal ones were all undetectable (<0.05 p.p.b.). Urine samples were collected for three other people present during the work simulation. Urinary 1,6-hexamethylene diamine, considered to be the most sensitive biomarker of HDI exposure [7], ranged from <1.0 to 15.4 μg/g creatinine (controller 1: 5.1, controller 2: <1.0, line manager: 4.0, investigation team member 1: <1.0 and 2, who had slight dermal contact with HDI: 15.4).

In February 2009, immunological investigations in the patient revealed raised specific IgG antibodies to HDI (2.9 mg/l) and to 4.4-diphenylmethandiisocyanate (3.2 mg/l) but not to toluene-2.4-diisocyanate (<2 mg/l), specific IgE antibodies and a lymphocyte transformation test were negative. Skin tests (prick, scratch and patch tests) were performed with TDI (Fluka art 89870) and HDI (Merck art 822066) at a dilution of 1:10 in phosphate-buffered saline (PBS; pH 7.4). PBS served as a negative control. Prick and scratch tests were negative. Patch tests showed a positive delayed skin reaction to HDI at 48 h. In the next 2 weeks, the patient developed eczema around her neck and shoulders, suggesting sensitization to HDI. After 22 days, a skin biopsy showed spongiotic dermatitis, with $CD4^+$ T cells infiltrating the dermis and $CD8^+$ T cells lying at the dermo-epidermal junction and in the epidermis compatible with a T-cell-mediated-delayed hypersensitivity reaction to HDI.

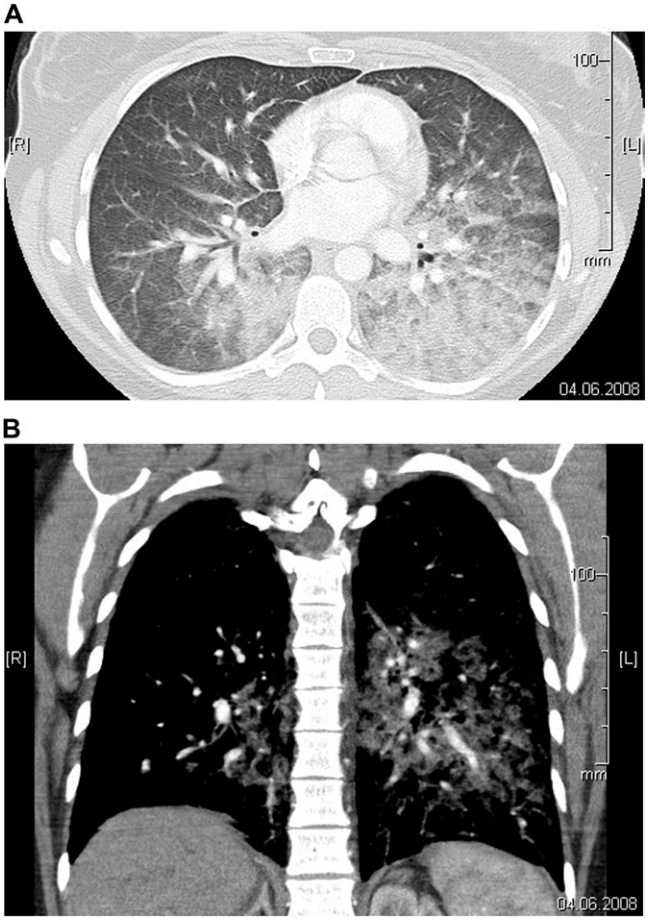

Figure 1. High-resolution computerized tomography at Day 1.

Discussion

This case suggests that low-level airborne HDI and possibly dermal exposure can cause EAA, possibly mediated by activated T cells.

The differential diagnosis of an acute respiratory event like this includes hemorrhagic pneumonitis, acute respiratory distress syndrome and idiopathic eosinophilic pneumonia. As neither bronchoalveolar lavage nor specific immunoglobulin tests were performed at the time of the incident, we performed occupational and immunological investigations and supported the diagnosis of EAA by using the clinical criteria of Lacasse *et al.* [8]. The following criteria apply in this case: (i) exposure to a known offending antigen, (ii) symptoms 4–8 h after exposure, (iii) respiratory crackles and (iv) positive serum precipitins. Criteria (v) recurrent episodes and (vi) weight loss did not apply in this case, but the probability of EAA is still 90%. As the incident was life threatening, we did not risk re-exposure or specific challenge test.

The moderate levels of IgG antibodies to HDI may reflect the lack of re-exposure to HDI for >6 months. The precise biological and clinical relevance of specific IgG in EAA remains unclear [1]. Allergy tests revealed a strong delayed-type reaction to isocyanates, which is characteristic for T-cell sensitization. Previous studies indicate that cellular hypersensitivity, including activated T cells may be relevant in the pathogenesis of EAA [9]. We observed marked infiltration of $CD8^+$ T cells at the dermo-epidermal junction and in the epidermis. Thus, in addition to inducing contact dermatitis, T cells may also infiltrate the lung and mediate alveolitis.

Low levels of airborne isocyanate exposure suggested that dermal contact might have significantly contributed to total body uptake, as suggested by recent studies [10], highlighting the importance of biological monitoring.

Key points

- This case report suggests that low-level hexamethylene diisocyanate exposure may induce life-threatening extrinsic allergic alveolitis.
- Hexamethylene diisocyanate skin absorption may have been a significant route of exposure.
- Effective control of occupational diisocyanate exposure requires both skin and respiratory protection.

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Conflicts of interest

None declared.

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