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Acute respiratory disorder, rhinoconjunctivitis and fever associated with the pyrolysis of polyurethane derived from diphenylmethane diisocyanate

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OBJECTIVES — A case is described of complex reactions associated with exposure to diphenylmethane diisocyanate (MDI), with some immunologic observations.

METHODS — Medical history, clinical examinations, and analyses of immunologic parameters and the 4,4'-MDI-related amine 4,4'-diaminodiphenylmethane (MDA) in hydrolyzed serum and urine were used.

RESULTS — The patient, a mechanic whose medical history suggested repeated attacks of a work-related pulmonary or systemic disease, was examined because of acute respiratory disorder, rhinoconjunctivitis, and a late systemic reaction after exposure to polyurethane pyrolysis products, including 4,4'-MDI (air level 15 μg·m⁻³). Spirometry showed a partly reversible obstructive dysfunction, and a skin-prick test was positive versus isocyanates conjugated with human serum albumin (HSA). MDA was detected in hydrolyzed serum (5.6 ng·ml⁻¹) and urine (1.6 μg·g creatinine⁻¹). In serum, there were specific immunoglobulin (Ig) G (IgGI and IgG4) and IgE antibodies to 4,4'-MDI-HSA and other isocyanates (phenylisocyanate, toluene diisocyanate, p-toluene monoisoocyanate, hexamethylene diisocyanate) conjugated with HSA, a very high total IgE, a raised total IgG, and moderate neutrophilia and eosinophilia. The specific antibodies declined, but were still increased five years later. Furthermore, the values of circulating immune complexes were high. In vitro, the circulating immune complexes in serum increased after the addition of 4,4'-MDI-HSA. The patient had anti-C1q antibodies, which probably accounted for part of the circulating immune complexes.

CONCLUSIONS — The reactions associated with MDI exposure (in combination with exposure to pyrolysis products) had features compatible with immediate hypersensitivity and with a complement-mediated immune-complex reaction.

KEY TERMS — allergy, hypersensitivity, isocyanate, immune complexes, isocyanate-specific IgE and IgG, lung disorder, occupational, systemic reaction.

Because of its low vapor pressure diphenylmethane diisocyanate (MDI) was originally considered to have a low potential to induce disease. However, in connection with spraying, or heating, MDI has been associated with both asthmatic and systemic reactions (1—4). The mechanisms behind these diseases are still controversial. Pharmacological, immunologic, and irritant mechanisms have been suggested. The present case report concerns clinical and immunologic aspects of the adverse reactions resulting from the heating of polyurethane (PU) resin, derived from MDI. The main component of technical grade MDI is normally the 4,4'-isomer.

Case

History. The patient was a 45-year-old mechanic. In 1976, he started to manufacture, assemble, and repair conveyer belts [made of PU, polyvinyl chloride (PVC), polyester, or natural fibers] in his workshop and in different factories. He joined PU or PVC belts using high-frequency welding or a homemade tool, which heated the material electrically to 150—170°C. He also imprinted belts with another homemade tool, a metal roller, while blowing hot air (350—600°C) on the surface of the belts.

The patient had never had any allergic manifestations. He was a smoker (about 30 cigarettes daily). In 1970 he had unilateral optic neuritis. In January 1984 he was hospitalized, after three weeks of coughing with hemoptysis, because of a pulmonary infiltrate in the right upper lobe. The infiltrate only gradually subsided after he was put on antibiotics. Bronchoscopy revealed generalized bronchitis. Two months later, he had a flu-like illness. In July 1986 he spent 24 h in the hospital under the diagnosis “virosis,” because of repeated attacks of myalgia,
fever, and shivering during the preceding fortnight. His temperature was 38.7°C at admission, (next morning 37.0°C). He had been working with isocyanate glue for about a week, and, on the day of hospitalization, had been joining PU conveyor belts.

In the beginning of November 1986, he had been imprinting on a PU-impregnated conveyor belt (19 x 0.4 m; PU surface 0.8 mm thick) for 5 h in a bakery. After work, he suffered from chest tightness. Between 1300 and 1500 in the afternoon on the 19th of November, he had again imprinted on the belt. He used no respiratory protective equipment. Fifteen minutes later he was struck with heavy respiratory distress, which lasted for about 30 min. He left the workplace with a sore throat, stuffy nose, and red eyes. At 2000, he was beginning to chill and shiver. At midnight, his temperature was 38.8°C and at 0600 the next morning it was 37.6°C. In the physical examination made at 0800, there was nose congestion, bilateral conjunctivitis, edema of the eyelids, and sparse crepitating rales on the left lung base. During the ensuing 10 d, the symptoms and signs gradually subsided.

Exposure. According to the PU conveyor-belt producer, the PU was supposedly derived from toluene diisocyanate (TDI). In January 1988, to confirm the alleged exposure, the patient (wearing a coal-filter respirator mask) experimentally repeated, in his workshop, the imprinting job he had done in the bakery. The smoke contained 170(0.2 m above the belt) ppm of all substances except MDI (same as in 1984), expected 4.3 mg/m³, but no TDI. (For the method see reference 5.) An 4,4'-MDI-related amine, 4,4'-diaminodiphenylmethane (MDA), but not the TDI-related amine, toluidinediamine, was detected in hydrolyzed serum (5.6 ng · ml⁻¹) and urine (1.6 μg · g creatinine⁻¹) on 20 November 1986 [as determined by gas chromatography and selected ion monitoring (unpublished observations and reference 6)]. Decreasing levels of MDA were found in serum and urine during the following months and days, respectively. (A bystander, without respiratory protection, exposed for 24 min during the afore-mentioned pyrolysis experiment in the workshop, had serum levels of 0.03 before the exposure and 2.7 ng MDA · ml⁻¹ 0.5 h after it.)

Clinical examinations. An X-ray of the lungs (20 November 1986) displayed slight atelectases on the left base, present already in 1984. Spirometry showed a vital capacity of 5.1 l (same as in 1984), expected 5.6 l, and a forced vital capacity in 1 s (FEV₁.₀) of 3.5 l (4.1 l in 1984), expected 4.3 l. The volume of trapped gas was 2.7% of the total lung capacity (upper reference limit 2.0%). The gas distribution and the carbon-monoxide diffusion-capacity were normal. In May 1987, as well as in January 1988, the FEV₁.₀ was again higher, 4.0 l (both times), and the vital capacity was 4.8 and 5.0 l, respectively.

Skin-prick tests with isocyanate [4,4'-MDI, phenylisocyanate (PhI), TDI, p-toluene monoisocyanate (p-TMI)], hexamethylene diisocyanate (HDI)] conjugates with human serum albumin (HSA) evoked positive responses to all of the substances (wheat at least half that induced by histamine). The skin-prick test with 13 common allergens was negative.

Routine laboratory tests. The erythrocyte sedimentation rate rose from 12 mm on November 20th to 22 mm on November 25th. Electrophoresis samples of serial blood revealed acute inflammatory activity and, especially, an increase in orosomucoid. On November 20th, the neutrophilic cell count was 7.9 · 10⁹ · l⁻¹ and had, on November 21st, decreased to 3.3 · 10⁹ · l⁻¹. Eosinophils reached a maximum of 0.8 · 10⁹ · l⁻¹ on November 21st and a base level of 0.2 · 10⁹ · l⁻¹ on December 8th. The total immunoglobulin (Ig) A and total IgM were maximal on November 25th, 2.55 and 1.5 g · l⁻¹, respectively, and 2.04 and 1.2 g · l⁻¹, respectively, on December 12th. The total IgG (figure 1) and, especially, the total IgE (figure 2) were elevated. There were no specific IgE antibodies against common allergens and no rheumatoid (Waaler-Rose) or antinuclear (ANA) antibodies. Much later, in 1993, Sjögren's syndrome (SS-A) autoantibodies were found.

Genetic typing. The patient's human leucocyte A type was A2, 24; B7; Cw7; DR2, 6. The phenotype of the complement protein C4 was C4A3, C4B1. He was a rapid acetylator (in Dapsone® and N-acetylation transpherase 2 genotype tests).

Immunologic analyses. Specific IgG (figure 1, ELISA [7]), and specific IgE [figure 2, RAST (7)] antibodies against 4,4'-MDI, PhI, TDI, p-TMI, and HDI conjugates with HSA were markedly increased. In addition, specific IgG (absorbance) and IgE (percentage of binding) antibodies against phthalic anhydride (PA) conjugate with HSA were elevated [IgG 1.3, upper reference limit 0.3; IgE 17, upper reference limit 0.3 (8)]. RAST (method from reference 9) and ELISA inhibition tests supported the specificity (IgE against isocyanates and PA, IgG against 4,4'-MDI-HSA). As to subclasses, IgG1 and IgG4, antibodies to isocyanate and PA were present at levels above normal; the absorbance values for IgG4 were at least 20 times for 4,4'-MDI, PhI, and p-TMI, and for IgG1 more than 10 times, the upper reference limit. The specific IgM isotype antibodies were low. (For the method see reference 8.)

The RAST values for specific IgE against 4,4'-MDI-HSA decreased after the end of the exposure (initial half-time one to two months), but they were
Figure 1. Serum levels of total immunoglobulin G (IgG), and specific IgG antibodies to conjugates of isocyanates and human serum albumin (HSA) in a patient exposed to diphenylmethane diisocyanate (MDI) (day 0 = 19 November 1986). (IgG MDI-HSA = specific IgG to 4,4'-MDI-HSA, IgG HDI-HSA = specific IgG to HDI (hexamethylene diisocyanate)-HSA, IgG TDI-HSA = specific IgG to TDI (toluene diisocyanate)-HSA, IgG p-TMI-HSA = specific IgG to p-TMI (p-toluene monoisocyanate)-HSA, IgG Phi-HSA = specific IgG to Phi (phenylisocyanate)-HSA, upper reference limit for total IgG = 12.6 g·L⁻¹, for specific IgG (absorbance) versus MDI-HSA, TDI-HSA, and p-TMI-HSA = 0.2 and versus Phi-HSA and HDI-HSA = 0.3; total IgG was measured only at dates as indicated — this is not a linear scale.)

Figure 2. Serum levels of total immunoglobulin E (IgE) and specific IgE antibodies to conjugates of isocyanates and human serum albumin (HSA) in a patient exposed to diphenylmethane diisocyanate (MDI) (day 0 = 19 November 1986). (IgE MDI-HSA = specific IgE to 4,4'-MDI-HSA, IgE Phi-HSA = specific IgE to Phi (phenylisocyanate)-HSA, IgE p-TMI-HSA = specific IgE to p-TMI (p-toluene monoisocyanate)-HSA, IgE HDI-HSA = specific IgE to HDI (hexamethylene diisocyanate)-HSA, IgE TDI-HSA = specific IgE to TDI (toluene diisocyanate)-HSA, upper reference limit for total IgE = 100 kU·L⁻¹, and for specific IgE isocyanate antibodies = 0.3% binding; total IgE (method: IMx assay, Abbott Laboratory By PRIST Pharma­cia, total IgE was 3705 kU·L⁻¹ on day 1) was measured only at dates as indicated — this is not a linear scale.)
still above the upper reference limit in September 1991 (day 1750 in figure 2). The ELISA values for IgG decreased even more slowly (figure 1). The IgG and IgE values versus TDI-HSA decreased somewhat faster.

No precipitating antibodies against 4,4'-MDI-HSA, TDI-HSA, or HDI-HSA were found in Ouchterlony analyses (3% weight/volume PEG6000 added to the gel). The complement proteins C1q, C1s, C3, and C4 in sera from 20 and 21 November 1986 were slightly increased. (For the method see reference 10). Circulating immune complexes were present above the normal range (C1q binding assay from reference 11; solid phase C1q binding assay, modified from reference 12). In vitro, the addition of 4,4'-MDI-HSA (figure 3), or TDI-HSA (not shown), in increasing concentrations up to 5 g·l⁻¹, gave a marked increase in the C1q binding activity in the serum. With samples obtained two and four years later, no such increase was seen, but the levels of circulating immune complexes in serum were high (figure 3).

The assessment of C1 activation [crossed immunoelectrophoresis (13)] showed an increased concentration of complexes containing C1 inhibitor, C1r, and C1s at the time of the exposure. In the sera obtained two and four years later, increased levels of complexes containing inhibitors of both (C1r-C1s)2 and C1 were observed. Incubation of sera with 4,4'-MDI-HSA did not result in C1 activation, neither were C3dg fragments generated. (For the method see reference 14). Furthermore, there was no cleavage of C3 after incubation with TDI-HSA [crossed immunoelectrophoresis (15)]. Anti-C1q antibodies were found in serial serum samples collected since the exposure, the highest concentration occurring four years after the exposure, 280 arbitrary units·ml⁻¹ (upper reference limit 16; method from reference 16).

To elucidate any constitutional deviation, we determined peripheral blood lymphocyte markers for CD2, CD3, CD4, CD8, and CD19 using flow cytometric analysis and found them to be normal in 1990, as was the stimulation of peripheral blood mononuclear cells (PBMC) with phytohemagglutinin or pokeweed mitogen. To study possible immunologic memory, PBMC and B-cell depleted PBMC (Dynabeads Pan-B [CD19], Dynal AS, Oslo) were incubated with 4,4'-MDI-HSA or with epoxy Mw 340 (DGEBA), but we found no stimulation of cells, as measured by the uptake of 3H-thymidin.

**Course of events.** After November 1986, the patient began to use respiratory protective devices whenever he thought he might be substantially exposed to isocyanates. In January 1988 (day 428 in figures 1 and 2), he was reexamined in the hospital because of skin rash and papular eruptions on his hands (present for one and a half months) and facial edema (present about 10 d). In connection with the onset of symptoms, he had started to use a new glue.
In the examination, he showed an intense patch-test reaction against epoxy Mw 340, but not versus MDA, MDI, or other materials that he had used.

In March 1992, he had repeatedly heated PU materials without respiratory protection (before day 1940, figures 1 and 2). In April (day 1969), he imprinted on a belt (of unknown composition) in a bakery and was struck with acute respiratory distress, sore throat, chills and fatigue, lasting for about 24 h.

**Discussion**

Already before the first examination for symptoms (November 1986), the patient had probably had repeated isocyanate-associated systemic reactions. The high values of specific immunoglobulins already in the very first blood samples at least indicated earlier exposure(s).

A noteworthy aspect is the inadequate information supplied by the manufacturer with regard to the composition of the conveyer belt. Thus the relevant isocyanate became fully clear only after an analysis of air, serum, and urine samples. The 4,4'-MDI-related amine, MDA, was detected in hydrolyzed serum and urine. In workers exposed to MDA as such, much higher levels (in urine) have been reported (17).

Furthermore, judged from the rough exposure measurements made later in the workshop, the exposure to MDI might have been below the permissible limit (in Sweden 50 μg·m⁻³, time-weighted average). However, even such exposure, at least to TDI, may cause disease (2, 4). In the present case, though, the exposure has been complex.

In spite of the known exposure to 4,4'-MDI only, the patient had specific IgG and IgE antibodies to a variety of isocyanates (the highest values, though, for 4,4'-MDI) and PA. This finding could be due to other exposures or to cross-reactivity, possibly because of new antigenic determinants being formed (2, 18-19).

The specific IgE and IgG antibodies gradually disappeared after the supposed end of peak exposure to MDI, in accordance with earlier studies of IgE and IgG isocyanate antibodies (19-20) and IgE antibodies to other small organic molecules (21). Apparently, the IgE level decreased faster than that of IgG. IgE versus TDI-HSA decayed more rapidly than IgE versus 4,4'-MDI-HSA, perhaps due to a lower affinity of the specific TDI antibodies. The decrease of the total IgE and IgG level was faster than that of the specific antibodies. Thus, in addition, there seems to have been a polyclonal activation of B cells.

We do not know with certainty that the demonstrated specific antibodies played a pathogenetic role for the respiratory and systemic reactions. IgE antibodies have earlier mainly been associated with isocyanate asthma (2-4, 22), recently also with isocyanate-induced hemorrhagic pneumonitis (23). Our patient had a complicated clinical picture; possibly his rhinoconjunctivitis and acute dyspnea were IgE-associated.

4,4'-MDI-HSA-specific IgG antibodies may be an index of exposure (3, 7, 22), but they may also be associated with asthmatic reactions (3-4, 24-25) and with a type III IgG-dependent hypersensitivity to MDI (19, 26), presented as a flu-like syndrome in the case of our subject. Humoral, as well as cellular, immunity may be involved in the pathogenesis of hypersensitivity due to isocyanates and other organic agents (3, 23, 27-29). The role of the IgG subclasses remains uncertain (7-8).

The patient had circulating immune complexes that bound C1q, and some increase in the complexes was observed after isocyanate conjugates were added to acute serum in vitro. This phenomenon might reflect the presence of antibodies related to the development of symptoms. The patient’s sera showed the presence of excess (C1r-C1s)2 complexes, also an earlier finding for patients with chronic urticaria or angioedema (30). Furthermore, IgG binding to collagen-like fragments of C1q was demonstrated in the sera. IgG reaction with C1q has been reported for patients with systemic lupus erythematosus (16, 31) and patients with hypocomplementemic urticarial vasculitis syndrome (16, 32). Our patient had neither of these diseases. The pathogenetic significance of C1q antibodies is not known (32). Possibly, our findings reflect an autoimmune response to antigenic stimulation from isocyanates. Anti-C1q antibodies have been suggested to be responsible for the majority of the solid-phase C1q-binding IgG in the sera of most patients with systemic lupus erythematosus (31), and such antibodies in our patient probably account for part of the circulating immune complexes (32). Decreased clearance of circulating immune complexes in the patient could not be ascribed to a deficiency of C4A, the C4 isotypemost efficient in processing immune complexes (33).

This case shows that isocyanate-associated disease has to be considered in cases with unclear respiratory and general symptoms and signs. The presence of specific antibodies was the main finding, and the complement system was probably also involved. The finding of antibodies to C1q suggests an autoimmune reaction; this reactivity may have influenced the patient’s symptoms. The presence (in 1993) of SS-A antibodies gives some further support to the possibility of an autoimmune disposition in this patient, as does his history of optic neuritis, a disease in which autoimmune mechanisms might be involved (34).

The mechanism behind isocyanate-related illness is still obscure. The present case might have a general bearing on mechanisms. It is possible that the features of our patient’s disease that seem unique are not really so — but have simply not been studied earlier. Our findings should form a basis for epidemiologic approaches. More basic information concern-
ing immunologic characteristics and predisposing host factors is certainly needed.

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Addition to proof
In 1994, the patient developed crescentic glomerulonephritis with autoantibodies against myeloperoxidase. This development underscores his autoimmune disposition. The significance of his isocyanate reactivity (in 1994 he still has IgE and IgG isocyanate antibodies), if any, is unknown.

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