Pulmonary Involvement in Zinc Fume Fever*

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A patient with the clinical history of recurring zinc fume fever underwent an experimental welding exposure; this resulted in a systemic reaction and a distinct self-limiting response in the periphery of the lung, demonstrated by pulmonary function tests and bronchoalveolar lavage. These pulmonary changes observed for the first time in man were reproducible.

Metal fume fever has been known for over a century as an occupational disease that is induced by intense inhalation of fresh metal fumes with a particle size smaller than 0.5 μm to 1 μm. The fumes originate from heating the metals beyond their boiling point, as happens, for example, in welding operations. Oxidation usually accompanies this process. In most cases, this syndrome is due to exposure to zinc oxide fumes; however, other metals like copper, magnesium, cadmium, manganese, and antimony are also reported to produce such reactions.¹,² The starting point of our investigations was a patient with the history of a recurring zinc fume fever. In this patient, we used pulmonary function tests and bronchoalveolar lavage to examine the changes in the pulmonary tissue following the inhalation of zinc oxide fumes generated in welding processes.

Case Report

Up until 1980, the now 26-year-old locksmith, a smoker (25 cigarettes per day), was well. In that year, he started a new job with much welding, usually without safety precautions such as a protective mask and adequate ventilation. A few hours after welding on zinc-coated materials for the first time, the patient developed shivering, sweating, and shortness of breath. Whatever welding technique he used, these complaints recurred many times when he was working with zinc materials. Other metals did not produce any symptoms. The discomfort always ceased spontaneously until the following day.

Clinical Findings

When referred to us, the patient was asymptomatic and had normal findings on physical examination, electrocardiogram, chest x-ray film, and all routine laboratory tests. Pulmonary function (equipment and methods, see König et al³) including inspiratory vital capacity (IVC), total lung capacity (TLC), airway resistance (Raw), forced expiratory volume in one second (FEV₁), transfer factor (single-breath method, Dsb), and blood gas levels at rest as well as during exercise gave normal results.⁴ Merely the inhalation challenge with methacholine revealed a low-grade nonspecific bronchial hyperreactivity (five breaths of a 3 percent nebulized methacholine solution increased the Raw from 0.22 to 0.57 kPa × s × mL⁻¹; a positive reaction is presumed in our laboratory when the Raw exceeds 0.35 kPa × s × mL⁻¹ and the increase is greater than 0.2 kPa × s × mL⁻¹).

Challenge Tests

With an interval of six months, we made two exposure tests under working conditions and laboratory control; the patient welded one hour on a zinc-coated tube with an electric torch. The fume was sampled in part by a constant flow sampler (Dupont model S 2300) for analysis. Blood levels of zinc and cadmium were measured after both tests (methods according to Stoeppler et al⁵ and Vieira and Hansen⁶).

Results

The Raw was slightly increased immediately after the welding process (Fig 1), but in one hour, it was in the normal range again without any treatment. Two hours after the end of the challenge, the patient experienced a sweetish taste, shortness of breath, and a chilling sensation; one hour later, there were pronounced chills, and three hours later, the patient showed profuse sweating.

With a maximum three to six hours after the end of the exposure, we found a significant reduction of the IVC (from 5.25 L to 3.1 L), Dsb (40 percent of initial value), and the arterial oxygen partial pressure (PaO₂, 9 mm Hg), while the body temperature was raised to 38.5°C and the peripheral blood leukocyte count to 24 g/L (Fig 1). The subsequent chest x-ray film and the findings from physical examination of the lungs were normal. On the day after the welding test, the patient was nearly asymptomatic, and the pulmonary function test results were without abnormal findings, except a slightly decreased Dsb (77 percent of the predicted value). A second trial, which was done after a six-month symptom-free interval with no contact to zinc fume welding on zinc-coated tubes, elicited a systemic and a pulmonary reaction of the same kind and degree as the first test.

The analysis of the sampled dust showed a high portion of zinc (2.0 mg of a total quantity of 6.12 mg), whereas only a small amount of cadmium, which often occurs as a contaminant in zinc and is feared because of its toxicity,⁷ could be found (0.024 μg). In accordance with that, the blood level of zinc was significantly increased after both tests, but the cadmium concentration was normal (Table 1). We performed two bronchoalveolar lavages as described previously.⁸ The first bronchoalveolar lavage was done one day after the second challenge test, when the patient was free of symptoms again and the pulmonary function tests all gave normal results. The total cell count of the lavage material was ten times as high as normal (total cell count, 94 × 10⁶), and the differential cell count showed a marked increase of polymorphonuclear leukocytes. Another bronchoalveolar lavage was performed after a period of seven weeks without any contact to zinc fumes. The total cell count (7.3 × 10⁶) and the differential cell

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count were now normal, but there was a striking polymorphism and polyneucleosis of many of the macrophages (Table 2; Fig 2 and 3). In both procedures the bronchial system was macroscopically normal, and no bacteria could be found in the fluid from bronchoalveolar lavage.

**DISCUSSION**

Taking into consideration the case history of the patient, the diagnosis of zinc fume fever is suspected. This is confirmed by the results of the two welding tests with zinc-coated materials; the patient developed self-limiting chills, fever, and dyspnea, and the zinc levels in the blood were clearly increased. Besides the reported symptoms a systemic reaction is indicated by the marked rise of the white blood cell count; pulmonary involvement is established by the distinct deterioration of IVC, Dsb, and PaO₂. Like the

**Table 1—Blood Levels of Zinc and Cadmium after Welding on Zinc-Coated Material**

<table>
<thead>
<tr>
<th>Data</th>
<th>First Test</th>
<th>Second Test</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood level of zinc, mg/L</td>
<td>6.9</td>
<td>7.0</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Blood level of cadmium, μg/L</td>
<td>2.8</td>
<td>3.2</td>
<td>≤3.2</td>
</tr>
</tbody>
</table>

**Table 2—Immune Effector Cells in Bronchoalveolar Lavage**

<table>
<thead>
<tr>
<th>Data</th>
<th>Alveolar Macrophages</th>
<th>Lymphocytes</th>
<th>Polymorphonuclear Leukocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>First BAL</td>
<td>52</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>Second BAL</td>
<td>95</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Normal value</td>
<td>91.6 ± 6</td>
<td>9.2 ± 5</td>
<td>1.6 ± 1</td>
</tr>
</tbody>
</table>

*First bronchoalveolar lavage (BAL) was performed 24 hours after challenge test; second was done after seven weeks without any contact with zinc fumes.
experiments of Amdur et al. who observed a time-dependent progressive decrease of the compliance in guinea pigs after inhalation of zinc oxide fume, this reaction reflects in the periphery of the lung.

Not only the pulmonary function test results give evidence of a pronounced pulmonary reaction; in the bronchoalveolar lavage that was done 24 hours after challenge, we observed a distinct increase of the total cell count and the number of the polymorphonuclear leukocytes. So for the first time, to our knowledge, a severe acute inflammation of peripheral bronchoalveolar structures following zinc fume exposure could be demonstrated in man. The results agree with earlier reported experiments in animals; Drinker and Drinker found a great number of polymorphonuclear leukocytes in the alveoli of cats with experimentally induced zinc fume fever that had been killed on the day following exposure to fumes. Turner and Thompson also described an intense infiltration of polymorphonuclear leukocytes in the lungs of guinea pigs 24 hours after inhalation of zinc fumes. Because of these observations, we conclude that the inhalation of zinc fumes induces in general a high-grade alveolitis. Up to now, the etiopathogenesis of metal fume fever has been unclear; the hypothesis of a metal fume-induced release of endogenous pyrogens from leukocytes was formulated by Pernis et al. Mori et al. assume that the inhaled metal oxides initiate an oxidative action in the blood because of their catalytic activity. McCord postulates the production of metal proteinates (composed of the inhaled particles and the damaged pulmonary tissue) that are recognized as antigens and lead to the formation of allergen-antibody complexes which cause the clinical syndrome. The previously described reaction in our patient, with delayed alterations of pulmonary function parameters combined with chills, fever, and leukocytosis, resembles that in patients with an acute attack of a hypersensitivity pneumonitis. This clinical similarity to a disease that is thought to be induced at least in part by immune complexes supports the theory of McCord; however, besides the fact that the first attack of zinc fume fever occurred on the first day of work, the bronchoalveolar lavage of our patient is not compatible with a hypersensitivity pneumonitis; certainly early in the course of an acute attack, a significant accumulation of polymorphonuclear leukocytes is found in the bronchoalveolar lavage, but simultaneously, in both acute and chronic disease, a lymphocytosis is observed in most cases.

Up to now, no pulmonary fibrosis has been observed following metal fume fever, but the exciting question remains whether in that syndrome the marked increase of polymorphonuclear leukocytes is really harmless to the pulmonary tissue, whereas in others, the adult respiratory distress syndrome or irreversible pulmonary fibrosis is the consequence.

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Pulmonary Aspergilloma Diagnosed by Fiberoptic Bronchoscopy

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We report a patient with pulmonary aspergilloma in whom the mycetoma was visualized and biopsied during fiberoptic bronchoscopy. To our knowledge, this is the first report of pulmonary aspergilloma diagnosed in this manner.

A n intracavitary mass seen on chest x-ray film with an air-crescent sign is highly suggestive of a aspergilloma. A