We report the case of a 35-year-old woman who developed pulmonary alveolar proteinosis requiring multiple lavage treatments, in association with household exposure to ventilation system dust comprised at least partially by a cellulose fire-resistant fibrous insulation material. Scanning electron microscopy with energy-dispersive x-ray analysis documented the presence of spectral peaks consistent with the insulation material in transbronchial biopsy tissue. The patient showed symptomatic improvement once exposure to the insulation material had ceased. We believe that this case demonstrates an unusual association with pulmonary alveolar proteinosis. This case emphasizes the broad differential diagnosis for this histologic injury pattern and the need to thoroughly investigate environmental exposures in patients with unexplained pulmonary disease. (CHEST 2000; 117:1813–1817)

Key words: energy-dispersive x-ray analysis; pulmonary alveolar proteinosis; pulmonary function tests; scanning electron microscopy

Abbreviations: BEI = backscattered electron imaging; EDXA = energy dispersive x-ray analysis; PAP = pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis (PAP) is a nonspecific injury pattern characterized by the accumulation of granular, acellular, periodic acid–Schiff-positive material within the alveolar spaces, leaving the interstitial tissues relatively free of inflammation or fibrosis. Radiographically, bilateral airspace opacities are seen, often resembling pulmonary edema. Restrictive defects are typically seen on pulmonary function tests. Electron microscopic examination of the granular material shows myelin figures and lamellar bodies, leading to the theory that PAP originates from a defect in alveolar macrophage function, leading to accumulation and impaired clearance of intra-alveolar metabolic products such as surfactant.1

PAP may be idiopathic, or associated with various clinical settings and industrial exposures, including toxic gas inhalation, aluminum and silica exposure, exposure to metal oxide dusts, and opportunistic infection.2 PAP thus may be regarded as similar to other injury patterns (such as diffuse alveolar damage or interstitial fibrosis) in that it represents a nonspecific, stereotyped response to lung injury, for which careful history taking and clinical data are required.

In this report, we describe an unusual association between PAP and exposure to a cellulose-based household insulation dust.

Case Report

A 35-year-old woman presented with productive cough and shortness of breath. The cough was associated with production of thick, yellow, tenacious secretions, sometimes as well-defined clumps. The symptoms were reported to be progressive over the last 3 years, with marked worsening over the 4 months prior to presentation. Over time, the symptoms had become associated with dyspnea on minimal exertion. Inhaled bronchodilators and a corticosteroid trial were given without significant improvement.

The patient’s medical history was significant for an episode of Mycoplasma pneumonia, which occurred approximately 4 months prior to presentation at our institution. The episode was treated with IV antibiotics, resulting in resolution of fever and malaise but not of the underlying productive cough or dyspnea. The episode was complicated by development of deep vein thrombosis of the left leg, requiring treatment with IV heparin and warfarin. One year prior to presentation, the patient had undergone laparoscopic Nissen fundoplication that successfully treated her marked recurrent gastroesophageal reflux that was refractory to medical therapy. Finally, for several years, she had been treated with antihistamines and topical nasal steroids for symptoms consistent with allergic rhinitis, although she had never been specifically tested for this.

The patient lived with her husband and three children, all of whom were asymptomatic. She was a teacher by profession. She did not smoke or use alcohol, and she used only prescribed medications. She had lived in a small town all her life, and there was no recent history of traveling. She had worked in the same school for several years and had lived in the same house for 8 years. She had no pets inside the house and no specific hobbies other than bicycle riding.

On further questioning, the patient revealed that a gray-colored dust constantly collected around the outlets of the central air conditioning system in her home. The accumulation of this dust required constant cleaning. The patient stated that she was the primary person who cleaned the bedroom where the dust accumulation was heaviest. The gray dust, she reported, had the same appearance as insulation material that had been professionally installed in her house 8 years before. It was revealed that 2 years prior to this evaluation, the patient’s house had been flooded, producing significant damage to the rugs, some of which took a long time to dry completely.

On physical examination, the patient was a well-nourished white woman experiencing recurrent and prolonged bouts of coughing during examination, which prevented her from finish-
The patient was subjected to whole lung lavages using repeated aliquots of 500 to 1,000 mL of saline solution warmed to room temperature. The material obtained showed a milky hue that progressively cleared as the lavages were sequentially repeated. Twenty to 30 L of saline solution were used to lavage each lung. Following this first lavage, there was significant symptomatic improvement lasting 4 weeks. A second and third set of lavages was performed over the next 6 months, following the return of symptoms.

Tissue from the patient was prepared for scanning electron microscopy with backscattered electron imaging (BEI) and energy-dispersive x-ray analysis (EDXA). Examined samples included centrifuged fluid material from the patient’s second therapeutic lavage, a sample of the fibrous material exuding from the ventilating outlets at the patient’s home, and 5–μm-thick sections cut from the patient’s transbronchial biopsy tissue. The fibrous ventilation material, which reportedly represented insulating material, was off-white in color, soft, and fibrous. All specimens were placed on separate carbon planchettes, given a thin coat of carbon by vapor deposition, and then subjected to scanning electron microscopy, BEI, and EDXA as described below.

The ventilating system material under scanning electron microscopy was seen to consist of innumerable long thin fibers that were BEI positive, and which ranged in thickness from 5 to 20 μm (Fig 2). EDXA of these fibers generally showed an elemental composition of Al-Si-S-CI-K-Ca, with occasional weak peaks for Na and P (Fig 3). Accompanying the fibers were numerous BEI-positive particulates, most of which were < 10 μm in diameter (Fig 2). Some of these particulates showed an EDXA composition similar to the fibers, but other compositions noted for the particulates were Si, consistent with silica, Mg-Si (talc), Al-Si, K-Al-Si, and Ca-S.

The patient’s transbronchial biopsy under scanning electron microscopy showed the alveolar and bronchial wall architecture reflective of the light microscopic appearance of the biopsy. Eight BEI-positive particles, generally ≤ 10 μm in diameter, were found in the biopsy specimen and characterized by EDXA as having the following elemental compositions: Ca-Al-Si (1 particle), Ca-Si (1), Na-CI-K (4), Si-P-S-Ca (1), and Mg-Al-Si-P-S (1). In addition, a single group of five or six weakly BEI-positive fibrous structures of about 10 to 20 μm in diameter (Fig 4) were present, with thickness generally 5 to 20 μm in diameter.
found. By EDXA, these structures showed distinct peaks for Si and S, with weak peaks for P, Cl, and Ca (Fig 5). EDXA of background (endogenous) lung tissue showed in some areas an unremarkable “noise” signal characteristic of organic composition, and in other areas, there were weak peaks for S, P, Ca and/or Si. Analysis of centrifuged debris from the patient’s lung lavage material was attempted, but was rendered uninterpretable due to the large amount of sodium chloride (Na-Cl)-positive material present, which contributed strong backscatter and spectrochemical signals under EDXA. None of the samples showed evidence of acute exposure to silica, or other inorganic particle pneumoconioses. Also, asbestos fibers were not detected. The characteristic myelin figures and lamellar bodies of PAP were not observed, since this requires the resolution capability of transmission electron microscopy, which was not performed in this case.

On request, the patient’s family obtained the name of the insulation material installed in her home several years prior (Nature Guard Insulation [now called Cocoon Insulation]; GreenStone/Louisiana-Pacific Corporation; Portland, OR). A material safety data sheet was obtained from the company; this sheet listed the major ingredient as cellulose (88% by weight), derived from wood. Other ingredients in the insulation material, and their approximate percentages, by weight, were boric acid (H3BO3), 10%; ammonium sulfate [(NH4)2SO4], 11%; guar gum, 3%; and monoammonium phosphate (NH4H2PO4), 2%. The insulation material was described as containing no asbestos or fiberglass. The data sheet listed respiratory and mucous membrane irritation and possible long-term pulmonary fibrosis as potential hazards of exposure; use of eye goggles and a National Institute of Occupational Safety and Health-approved dust respirator were recommended in the handling of the material.

On the completion of the lung lavages and her return home, the patient obtained professional cleaning of the ventilation system in her house. This effort substantially reduced the leakage of the fibrous insulation material through the central air system. Concomitantly, the patient experienced progressive relief of her symptoms, which has lasted 9 months. Changes in the patient’s pulmonary function studies over time are shown in Table 1.

The patient’s general tendency to improvement was punctuated by symptomatic exacerbations requiring lavages at 8 months and 13 months after first presentation. An open lung biopsy was performed at the latter time, which showed persistent PAP. There was no evidence of superimposed infection or other significant findings. Scanning electron microscopy with EDXA showed only rare incidental endogenous and exogenous particles. No fibrous structures or elements were identified that would be compatible with the ventilation system dust that had been observed in the earlier biopsy. Thus, the results were consistent with reduced or eliminated exposure to the dust, presumably from the cleaning efforts the patient had undertaken. Following the latest lavage, the patient improved, and she remains free of significant symptoms to date, 16 months after first presentation.

**DISCUSSION**

In this case, silicon and other spectral peaks were detected in the transbronchial lung biopsy tissue (Fig 5),
which resembled the EDXA spectrum of the ventilation material comprising the patient’s exposure (Fig 3). Silicon is particularly noteworthy because it is detectable in many exogenous dusts but not normally in endogenous lung tissue. The element should be distinguished from silica (SiO₂), the crystalline form of which may result in a PAP pattern if inhaled in very high doses. Figure 4 shows 10 to 20 μm in diameter fibrous structures with distinct EDXA peaks including Si (Fig 5), although weaker peaks for these elements were also observed at other areas in the lung tissue. Thus, these fibrous structures represent either actual inhaled fibers, or endogenous structures (collagenous or muscular) that have been impregnated with materials (perhaps dissolved) from the ventilation dust. Silicon, aluminum, calcium, potassium, sodium, and chlorine, all of which were detected in vitro in the insulation material, have been detected by EDXA in inhaled fibers derived from wood. It is also known that plants contain biogenic forms of silica, known as phytoliths, that produce a silicon peak on EDXA. It is also possible that the ventilating system dust contained other substances from the ventilating system besides the insulation material in question (this might explain the detection of silica, talc, and silicates in the ventilation dust by EDXA). Sulfur detected in these fibers comes from ammonium sulfate, and phosphorus from monoammonium phosphate, used as ingredients in the insulation. Fluorine is only weakly detectable by EDXA, and thus its presence in very small amounts in the insulation rendered our method insensitive to it. Other elements in the insulation (H, B, C, N, and O), all of less than atomic number 9, are not detectable by standard EDXA equipment.

Table 1—PAP Changes in Pulmonary Function Tests

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<tr>
<td>FVC, L</td>
<td>2.38 (63)</td>
<td>2.83 (75)</td>
<td>2.56 (68)</td>
<td>2.92 (78)</td>
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<tr>
<td>FEV₁, L</td>
<td>1.90 (64)</td>
<td>2.27 (76)</td>
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<td>2.28 (77)</td>
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<tr>
<td>RV, L</td>
<td>1.06 (63)</td>
<td>0.79 (47)</td>
<td>1.15 (67)</td>
<td>1.13 (67)</td>
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<tr>
<td>TLC, L</td>
<td>3.44 (63)</td>
<td>3.81 (70)</td>
<td>3.81 (70)</td>
<td>4.05 (74)</td>
</tr>
<tr>
<td>Dlco, mL/min/mm Hg</td>
<td>12.2 (54)</td>
<td>15.7 (71)</td>
<td>15.8 (71)</td>
<td>16.0 (73)</td>
</tr>
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*Data are presented as No. (percent of normal predicted); lavages were performed in July 1998, August 1998, February 1999, and July 1999; RV = residual volume; TLC = total lung capacity; Dlco = diffusing capacity of the lung for carbon monoxide.

Figure 5. EDXA spectrum of lung tissue taken at spot marked by asterisk (*) in Figure 4.

To our knowledge, no specific relationship between Mycoplasma infection and PAP has been reported; thus, the patient’s previous pneumonia appears unrelated. Also, we have not encountered previous reports of PAP in association with this type of insulation material. However, PAP has been reported in association with glass fiber dust in an animal model. Though the patient (by history) appeared to have suffered more exposure than other family members, it is otherwise not clear why she alone developed PAP. The probable reason is that PAP development is reflective of an individual’s immunologic susceptibility, and thus has different thresholds across different patients. Animal mod-
els have shown, for example, that PAP is elicited at different exposure thresholds to titanium dust, with a small proportion of rats never developing PAP even at the highest levels of exposure.7

Though the patient tended overall toward improvement, she required repeat lavages 8 months and 13 months after first presentation, despite the elimination of dust exposure at home. A lung biopsy at the latter time showed persistent PAP. Probably the reasons relate to an ongoing immune process in the lungs that has outlasted the initial exposure. Consistent with this is the observation that the function of alveolar macrophages is suppressed by the accumulation of the lipoproteinaceous debris in PAP,1 resulting in a self-perpetuating process. It remains to be seen if the reported elimination of the dust exposure at home will result in a permanent clearing of the patient’s PAP over time.

In summary, we report a case of PAP associated with household exposure to fibrous insulation material; evidence for the association came from clinical and pathologic (electron microscopic) grounds. Though it is possible this association could be merely incidental, the patient did experience gradual symptomatic improvement (albeit with two recent exacerbations requiring lavage treatments) once efforts were undertaken to remove the insulation dust exposure. This case emphasizes the importance of a careful clinical history in patients who present with unexplained, nonspecific pulmonary histologic injury patterns.

Unusual environmental associations may be uncovered in such cases, which prove useful therapeutically.

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REFERENCES