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Three Canadian farmers, including a married couple and another close relative, died from progressive pulmonary fibrosis. Their histories and investigations were compatible with chronic farmer's lung (FL). Our environmental and immunologic studies indicate Penicillium brevicompactum and P. olivicolor as probable new antigens of FL in a cool and dry climate. (CHEST 1997; 111:245-48)

Key words: antigens; extrinsic allergic alveolitis; farmer's lung; hypersensitivity pneumonitis; Penicillium brevicompactum; P. olivicolor; P. viritneum; pulmonary fibrosis

Abbreviations: FL=farmer's lung; HP=hypersensitivity pneumonitis; IFA=indirect fluorescent antibody

Fatal cases of farmer's lung (FL) are rare,1 and follow-up studies on patients with FL have shown that most can continue farming without severe irreversible lung damage.2 There is currently, however, insufficient evidence to predict the prognosis. We present three fatal cases of FL induced by new antigens and discuss factors relating to poor prognosis.

CASE REPORTS

CASE 1

A nonsmoking farmer had respiratory symptoms from the age of 30 years. The diagnosis of FL was made in January 1964, when he consulted a physician for chills, fever, cough, and dyspnea occurring several hours after exposure to moldy hay. A chest radiograph then showed diffuse fine nodular infiltrates (Fig 1,A). He was seen at the time of follow-up during winter or early spring with the same symptoms until 1971. He continued farming, but the acute episodes disappeared. In 1982, he again sought medical attention with complaints of dyspnea on exertion, and a chest radiograph revealed fibrotic changes. He moved from the farm to a nearby town, but continued farming periodically until he began receiving long-term home oxygen therapy in 1991. In 1993, he entered the hospital, and a chest radiograph showed end-stage honeycomb fibrosis (Fig 1,B). He never had demonstrable precipitating antibodies to common FL-related antigens (Thermoactinomyces, Aspergillus, etc.). Steroid therapy had little effect. He died of progressive respiratory failure in March 1994 at the age of 79 years. An autopsy was performed (see Pathologic Findings section).

Fatal Cases of Farmer's Lung in a Canadian Family*

Probable New Antigens, Penicillium brevicompactum and P. olivicolor

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FIGURE 1. Chest radiographs of case 1 in 1964 (A, left) and in 1993 (B, right).

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In 1986, the nonsmoking wife of the patient in case 1 had no symptoms of FL, but her chest radiograph showed diffuse fine nodular infiltrates. In March 1989, she consulted a physician for low-grade fever, shortness of breath, easy fatigability, and weight loss. A chest radiograph showed diffuse subpleural nodular infiltrates that had the appearance of ground glass. Her progressive dyspnea was worse in winter, and she developed subpleural patchy infiltrates on chest radiographs. She assisted with farm work as necessary until she began receiving long-term home oxygen therapy in 1992; at that time, the lungs had a honeycomb appearance. She had no demonstrable precipitating antibodies to common FL antigens. An open-lung biopsy was done in November 1993. There was temporary improvement in her symptoms and exercise tolerance while she was receiving prednisone therapy. Follow-up studies were done on an outpatient basis until her sudden death of unknown etiology in April 1994 at the age of 66 years. Postmortem examination was not performed.

**Case 3**

A brother of the patient in case 1 worked with him on the same farm from childhood. Patient 1 noted that his brother had had recurrent flu-like episodes; he had these episodes frequently at the same time as patient 1 had them. This patient retired in 1968 because of shortness of breath on exertion. His respiratory symptoms were stable for the next 20 years. When he sought medical attention in 1991 because of increasing dyspnea, his chest radiograph showed honeycombing. An open-lung biopsy was performed in June 1992. He was treated with long-term home oxygen therapy and prednisone, which could not control his progressive respiratory failure. He died in March 1994 at the age of 76 years. Postmortem examination was not performed.

In none of the cases was there any history of other lung disease, systemic disease, or exposure to toxic gases, fumes, or chemicals other than commonly used pesticides.

**Pathologic Findings**

The following findings were common to all cases: (1) marked interstitial fibrosis and cystic changes; honeycomb lung; (2) lymphoplasmacytic interstitial infiltration; (3) pericyctic/penumbrolial lymphoplasmacytic infiltration; (4) intracytic multinuclear giant cells (usual foreign body type). There was no evidence of granuloma formation, vasculitis, or infectious organisms in any of the cases.

**Environmental and Immunologic Findings**

Environmental and immunologic examinations were performed as previously reported. We collected dust samples from the farm, the farm house, the house in town that the patients in cases 1 and 2 lived in until their deaths, and from a disease-free farm in Saskatchewan, Saskatoon, Canada, in November 1993 and May 1994. Serum samples were available only from the patients in cases 1 and 2. Six antigens were extracted from the November dust samples with Coca’s solution. Gel double-diffusion method was performed on the 30 antigens shown in Table 1. The dust samples and 43 strains of microorganisms isolated from the environment were screened by the indirect fluorescent antibody (IFA) method. Culture-filtrate antigens were also prepared from five fungi that showed the highest titers by IFA as seen in Table 2.

Case 1 showed the densest precipitins to the antigen from the hay of the patient’s farm, and reactions to other prepared antigens (Table 1) were positive. In case 2, only the reaction to the hay was positive. Two Penicillium species dominantly cultured from the hay showed the highest IFA titers in both patients (Table 2). We identified the most probable antigens as *P. brevicompactum* and *P. olivaceor* at Japan Food Research Laboratories, according to a classification by Pitt in 1979.

In cases 1 and 2, the diagnosis of FL was made on the basis of symptoms related to hay exposure, radiologic and pathologic findings compatible with FL, antibodies positive to environmental dust and microorganisms, and the lack of evidence for alternative diseases. In case 3, our diagnosis was pulmonary fibrosis probably as a result of FL, since there were no findings that ruled out FL or supported other diagnoses.

**Discussion**

FL is a complex syndrome resulting from exposure to a large number of antigens varying with local climate, season, geography, or style of farming. The diagnosis involves documenting symptoms related to the antigen exposure and evidence of clinical, radiologic, and pathologic findings compatible with FL. Although appropriate serologic tests are an important aid in establishing the diagnosis, the antigen panels practically used in clinical laboratories are composed of up to ten antigens and are uniform in widely dispersed countries and regions.

In Saskatchewan, FL has been considered a rare disease. This is because the cool and dry weather inhibits the growth of FL-related microorganisms in hay and because most patients suspected of having FL do not have precipitating antibodies to the common antigens used for clinical tests.

There is currently no laboratory indicator to predict the

**Table 1—Environmental and Immunologic Findings With Gel Double-Diffusion Method**

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Antigens</strong></td>
<td></td>
</tr>
<tr>
<td>Hay from the patients’ farm*</td>
<td>+</td>
</tr>
<tr>
<td>Hay from a disease-free farm in Saskatchewan*</td>
<td>+</td>
</tr>
<tr>
<td>Mixed dust from grain elevators in Saskatchewan*</td>
<td>+</td>
</tr>
<tr>
<td>Smut fungus, <em>Ustilago scabra</em>, an antigen of HP†</td>
<td>+</td>
</tr>
<tr>
<td><strong>Negative Antigens</strong></td>
<td></td>
</tr>
<tr>
<td>Farm house dust*</td>
<td>–</td>
</tr>
<tr>
<td>Patients’ current house dust*</td>
<td>–</td>
</tr>
<tr>
<td>Oat dust*</td>
<td>–</td>
</tr>
<tr>
<td>4 antigens of HP* (<em>Candida albicans</em>, <em>A. fumigatus</em>, <em>Trichosporon asahii</em>, <em>T. mucosum</em>), 5 HP related antigens† (<em>Mucor sp</em>, <em>Bacillus sp</em>, A. niger, <em>T. pullus</em>, hay from a farm in Kumamoto, Japan), 14 commercially available antigens§ (<em>Thermoactinomyces vulgaris</em> #1, #2, <em>Microspordora faeni</em>, <em>Trichoderma viride</em>, <em>Sitotobius granarius</em>, <em>Cryptosporia corticale</em>, <em>Cephalosporium acremonium</em>, <em>A. fumigatus</em>, <em>A. clavatus</em>, <em>A. glaucus</em>, <em>A. niger</em>, <em>A. nidulans</em>, <em>A. sydowi</em>, <em>A. terreus</em>)</td>
<td></td>
</tr>
</tbody>
</table>

*Antigens prepared in this study.
†This antigen was negative in 10 healthy nonrelated control subjects and in 10 patients with summer-type HP.
‡Antigens prepared previously from environments of HP patients.
§From Hollister-Stier, Spokane, Wash.

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outcome in FL.\textsuperscript{2} Clinically, symptoms occurring for more than 1 year before diagnosis,\textsuperscript{1} evidence of pulmonary fibrosis at the time of diagnosis,\textsuperscript{1} and symptomatic recurrence\textsuperscript{9} have been reported to indicate a poor prognosis. Early diagnosis is important to maximize a favorable patient outcome. False negative results due to lack of appropriate antigen selection in serologic testing will delay the diagnosis. Laboratories, then, must select antigens based on knowledge of local climate and agricultural practices rather than rely on commercially available antigen panels.

No fatal case was reported in the major follow-up studies on FL after 1980: 29 cases with a 10-year follow-up,\textsuperscript{10} 61 cases with 1- to 11-year follow-up,\textsuperscript{11} 56 cases with 5-year follow-up,\textsuperscript{12} 101 cases with 5-year follow-up,\textsuperscript{13} and 33 cases with 6-year follow-up.\textsuperscript{2} Recently, Kokkarinen et al\textsuperscript{1} reported 13 cases of fatal FL in the 1980s in Finland and calculated the mortality rate due to FL as 0.7% from death certification and incidence data. The deaths occurred an average of 8 years after the diagnosis, and the length of symptoms was 12.1 years (range, 3.3 to 26 years). This is almost the same as the length of symptoms for the average of 17 years after diagnosis in the other 13 fatal cases in 1979.\textsuperscript{14} In the present cases, the time of onset was unclear, but the patients were symptomatic for 8 to 30 years. Therefore, we suggest the continued follow-up of patients with the risk factors just mentioned, even during symptomatic remission or after retirement.

The environmental and immunologic studies indicated \textit{P. brevicaespactum} and \textit{P. olivicolor} as probable new antigens of FL in a cool and dry climate. Penicillium is a universal saprophyte and produces abundant spores (conidia) smaller than 5 μm. It is plentiful in cooler climates, especially the cool temperature zone. \textit{P. brevicaespactum} is able to grow at the lowest temperature and water activity among fungi (–2 to 5°C and 0.78 a_w, respectively) and is frequently isolated from soil, decaying vegetation, food, cereals, etc.\textsuperscript{15} \textit{P. olivicolor} is rare but is a synonym of \textit{P. viridicatum}, which is commonly associated with cereal grain grown in cooler climates.\textsuperscript{15} In Canada, Penicillium is one of the most dominant microorganisms in the settled dust in grain elevators,\textsuperscript{16} swine buildings, and peat moss factories.\textsuperscript{17} In Sweden, most particles in air samples from 79 farms were spores from Actinomycetes, Aspergillus, and Penicillium, especially \textit{P. verrucosum} and \textit{P. brevicaespactum}.\textsuperscript{18}

In this report, trace precipitins were proved to the culture-filtrate antigens from \textit{P. brevicaespactum} and \textit{P. olivicolor}. This may be due to steroid medication the patients were taking at the times of serum collection. Also, the method for antigen preparation was not suitable to raise conidial antigens, since we have observed conidia of the present species to be eight times more reactive to patients’ sera than conidiophores by the IFA method.

In conclusion, we propose \textit{P. brevicaespactum} and \textit{P. olivicolor} as the probable causes of fatal FL. We suggest that delayed diagnosis was a factor in the fatal outcomes and that antigen selection in serologic testing should be appropriate for the local climate and farming practices.

ACKNOWLEDGMENTS: The authors thank Dr. Dheda (Outlook Union Hospital) for patient’s references, Dr. Udagawa and Mr. Anaka for identification of the isolates and mycologic advice, Dr. Kitaich for pathologic advice, Ms. McCulloch (Patient Information Services, Research Section, Royal University Hospital) for providing health records, and Ms. Remie and Ms. Day for general assistance.

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<table>
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<tr>
<th>Microorganisms</th>
<th>Source</th>
<th>IFA titer</th>
<th>Preciptins</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Case 1</td>
<td>Case 2</td>
</tr>
<tr>
<td>\textit{P. brevicaespactum}\textsuperscript{*}</td>
<td>Dominant from patients’ hay of November</td>
<td>1:256</td>
<td>1:256</td>
</tr>
<tr>
<td>\textit{P. olivicolor}\textsuperscript{*}</td>
<td>Patients’ hay of November</td>
<td>1:256</td>
<td>1:256</td>
</tr>
<tr>
<td>Fungus A (not identified)</td>
<td>Patients’ hay of November</td>
<td>1:128</td>
<td>1:128</td>
</tr>
<tr>
<td>Fungus B</td>
<td>Patients’ hay of May</td>
<td>1:128</td>
<td>1:64</td>
</tr>
<tr>
<td>Fungus C</td>
<td>Patients’ hay of November</td>
<td>1:128</td>
<td>1:32</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Cross-absorption test between the two species with serum of case 1 showed partial absorption of each other.
Succinylcholine-induced Hyperkalemia Following Prolonged Pharmacologic Neuromuscular Blockade*

Boaz A. Markowitz, MD; and Mark R. Elstad, MD

While being treated for the acute respiratory distress syndrome, a 27-year-old woman developed profound hyperkalemia and cardiac arrest following the administration of succinylcholine chloride (SCh). She had none of the risk factors previously described for development of severe hyperkalemia following SCh administrations; however, she had been intermittently treated with nondepolarizing neuromuscular blocking drugs throughout the course of her illness. We suggest that immobilization of critically ill patients with pharmacologic neuromuscular blockade may predispose them to severe hyperkalemia and cardiac arrest following administration of SCh. SCh should be used with great caution in such patients. (CHEST 1997; 111:248-50)

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Key words: cardiac arrest; hyperkalemia; immobilization; neuromuscular blockade

Abbreviations: AChR = acetylcholine receptor; IV = intravenously; SCh = succinylcholine chloride

Neuromuscular blocking agents are life-saving drugs in emergencies and have a limited, but important, role in facilitating mechanical ventilation in selected patients. Unfortunately, prolonged muscle weakness and other important adverse effects have been described with these agents. Succinylcholine chloride (SCh) has been reported to cause severe hyperkalemia in patients with burns, trauma, severe infection, or a variety of neurologic conditions. The patient presented herein had hyperkalemia and a cardiac arrest within minutes following the administration of SCh. She did not have any of the risk factors for this response that have previously been reported. We propose that the prolonged use of nondepolarizing neuromuscular blocking agents along with immobility and disuse atrophy predisposed her to this adverse drug reaction.

Case Report

A 27-year-old woman was admitted to another hospital with chickenpox and respiratory failure requiring mechanical ventilation. On hospital day 6, she developed a leak in the endotracheal tube cuff and was reintubated after receiving midazolam (5 mg, IV), vecuronium bromide (0.5 mg, IV), and SCh (110 mg, IV). Tracheostomy was performed on hospital day 10. Two days later, she was transferred to the University of Utah Medical Center Medical ICU for management of severe acute respiratory distress syndrome. She was paralyzed with vecuronium bromide during transport. The patient was treated with acetylsalicylic acid, mechanical ventilation, and parenteral nutrition. Initial ventilator management required the use of 100% inspired oxygen and high positive end-expiratory pressure. A standard tracheostomy tube was replaced with an endotracheal tube through the tracheostomy because tracheal injury and dilation, in combination with high airway pressures, resulted in a large air leak around the tracheostomy tube balloon. Between hospital days 14 and 25, she was heavily sedated and paralyzed with intermittent boluses of pancuronium bromide or vecuronium bromide to facilitate mechanical ventilation.

On day 31, the chronic air leak around her endotracheal tube cuff worsened and caused agitation, respiratory distress, hypercarbia, and respiratory acidosis. An attempt to blindly advance the endotracheal tube, which was 2 cm proximal to the desired position, was unsuccessful. The patient was sedated with 2 doses of midazolam (4 mg, IV), was paralyzed with SCh (100 mg, IV), and the tube was advanced over a fiberoptic bronchoscope without difficulty. While the bronchoscope was still in the endotracheal tube, the patient developed a wide-complex tachycardia followed by ventricular fibrillation and asystole. Advanced cardiac life support was immediately started, samples for arterial blood gases and serum electrolytes were sent to the laboratory, and treatment for presumed hyperkalemia (IV administered calcium gluconate, insulin, and glucose) was instituted. Arterial blood gas determination at that time revealed pH, 7.35; PaCO₂, 67 mm Hg; and PaO₂, 72 mm Hg; serum electrolyte values showed K⁺ to be 13.1 mEq/L. There was no evidence for hemolysis of the specimen; 20 min after cardiac arrest, her rhythm returned to sinus tachycardia in response to treatment for hyperkalemia and advanced cardiac life support. Another sample