Mycobacterium avium Complex Infection in an Immunocompetent Young Adult Related to Hot Tub Exposure*

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An unusual case of Mycobacterium avium complex infection occurred in a young adult with no preexisting disease and no evidence of immunodeficiency. There was diffuse interstitial involvement of the lungs which suggested an active alveolitis. Diagnosis required open-lung biopsy. Restriction fragment length polymorphism analysis and multilocus enzyme electrophoresis indicated that the source of the infection was a hot tub. The infection proved to be exceptionally responsive to treatment, and there was complete resolution with a four-drug regimen.

(CHEST 1997; 111:242-45)

Key words: drug susceptibility; Mycobacterium avium complex infection; restriction fragment length polymorphism

Abbreviations: MAC = Mycobacterium avium complex; RFLP = restriction fragment length polymorphism

Mycobacterium avium complex (MAC) infections have been most commonly found in older male patients with preexisting pulmonary disease1 or as a disseminated infection in patients with AIDS.2 Pulmonary infection in the absence of predisposing conditions has been recognized in a small number of older female patients.3 The case presented herein has unusual features which differentiate it in important respects from those cases previously reported. After detailed clinical studies, the patient, a young woman, appeared to have no significant respiratory or other illness and no abnormalities of immune function. She had a rapidly progressive course, with diffuse pulmonary changes suggesting alveolitis rather than an infection.

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Manuscript received April 2, 1996; revision accepted July 12.

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Diagnosis was arrived at only after open-lung biopsy. Restriction fragment length polymorphism (RFLP) testing indicated that the MAC infection was acquired from a hot tub.

CASE REPORT

A 20-year-old female student was referred to the senior author on February 3, 1995, with a spasmodic cough and breathlessness on minor exertion that became progressively worse since early December 1994. There was no fever, but she had lost some weight. She had recently noted a skin rash. She was a nonsmoker. There was a history of asthma in infancy, but this had not recurred. There was a hot tub that she used frequently in her home. Examination revealed scaly erythematous skin lesions on the neck, arms, and chest. There was no clubbing. The lungs were clear with no crackles or wheezes. Routine laboratory tests disclosed no abnormalities.

Chest radiographs showed a fine nodular pattern increasing in extent to occupy the mid and lower zones of the lungs. Pulmonary function tests revealed a mildly reduced vital capacity (76% of predicted) and a markedly reduced diffusing capacity for carbon monoxide (33% of predicted). The flow-volume tracing showed a nonobstructive pattern. With the patient breathing air, arterial blood gas levels showed a PCO₂ of 32 mm Hg, PO₂ 83 mm Hg; O₂ saturation, 97%; pH 7.43. An ECG and an echocardiogram were normal. A high-resolution CT scan revealed diffuse involvement, apex to base, with an infiltrate that had the appearance of ground-glass (Fig 1). There was no lymphadenopathy.

Angiotensin-converting enzyme was slightly elevated. Tests for

Figure 1. High-resolution CT scan. Basal section showing diffuse infiltrates with ground-glass appearance.
antinuclear factor, glomerular basement membrane antibody, and antineutrophilic cytoplasmic antibody were negative. Precipit
in tests for a variety of antigens were negative, but there was a
weakly positive reaction to Aspergillus and a positive reaction to
Pullularia. A test for HIV antibody was nonreactive.

After the initial investigation, she was advised to stop using the
hot tub, and this was drained and cleaned. She showed, never-
evertheless, a progressive deterioration over the next month, and on
March 1, 1995, she underwent an open-lung biopsy; a specimen
was removed from the lingula.

Microscopic examination of this specimen showed numerous
small nonnecrotizing granulomas scattered irregularly through-
out the lung with no tendency to be concentrated in the
centri lobular regions or along the lymphatic pathways (Fig 2).
Occasional respiratory bronchioles contained polyoid granulo-
matous lesions in which there was a minor element of fibrosis; the
appearance was suggestive of bronchiolitis obliterans. The adja-
cent alveoli contained large groups of foamy macrophages. Six
acid-fast bacilli were identified within the granulomas in sections
stained by the Ziehl-Neelsen method.

An intradermal test with 5 tuberculin units of purified protein
derivative S was negative. On the basis of the pathology report,
therapy was started with four drugs: isoniazid, rifampin, pyrazi-
namide, and ethambutol. She was discharged from the hospital
after 1 week with improvement in her cough and breathlessness.

On April 3, 1995, the organism in the lung specimen was
identified as MAC, and isoniazid and pyrazinamide were re-
placed by clarithromycin and ciprofloxacin. Therapy with ri-
fampin and ethambutol was continued. While receiving this
regimen, she showed progressive improvement; by May 31, 1995,
she was back to normal; cough and dyspnea were not present, the
skin changes cleared, and a normal flow-volume curve was
present. The chest radiograph showed complete clearing, and
another CT scan on June 8, 1995, showed no evidence of the
previous interstitial infiltrate. At a follow-up visit on February 3,
1996, after 11 months of treatment, she was asymptomatic, and
her chest radiograph showed no abnormalities. It was planned to
stop treatment after another month.

This improvement occurred despite the fact that sensitivity
testing at the regional mycobacteriology laboratory showed resis-
tance to all agents except streptomycin and amikacin. As a
consequence, a subculture was sent to the mycobacteriology
laboratory of the National Jewish Center in Denver. Using a
radiometric method (Bactec), the organism was reported to be
sensitive, or moderately sensitive, to clarithromycin, clofazimine,
ciprofloxacin, and ethambutol, although it was resistant to ri-
fampin. On testing with the combination of rifampin and etham-
butol, the minimal inhibitory concentration for rifampin was
reduced from 8 to 2 μg/mL and that for ethambutol was reduced
from 4 to 1 μg/mL, indicating a synergistic interaction.

After MAC was isolated in the lung, the hot tub was refilled
and operated for 1 week at 39.4°C. A 60-mL sample was
cultured, and a few colonies of MAC grew. This and the lung
isolate were sent to the mycobacteriology laboratory of the
Centers for Disease Control for further testing. Both isolates
were identified as *Mycobacterium avium* by multilocus enzyme
electrophoresis and had identical enzyme profiles. Further
characterization by RFLP analysis using the insertion sequence
IS1245, specific for *M avium*, showed a high degree of related-
ness between the isolates, suggesting they were essentially clonal.
The isolates had 25 to 30 matching copies of the insertion
sequence; the hot tub isolate contained at least three additional
copies (Fig 3).

A detailed immune study was carried out after 2 months of
therapy but showed no abnormalities. She had normal numbers
of CD4 and CD8 T lymphocytes with a normal response to
phytohemagglutinin stimulation; B lymphocytes were enumer-
ated and were normal. Anergy screening showed a reaction to
tetanus, diphtheria, and mumps, but no reaction to repeat testing
with tuberculin.

**DISCUSSION**

The febrile course in this case, with a clinical picture of
nonproductive cough and progressive breathlessness, as-
associated with a diffuse ground-glass radiographic pattern,
suggested that we were dealing with an active alveolitis,
possibly a hypersensitivity pneumonitis. Pullularia, for
which there was a positive precipitin test, has been
identified in allergic reactions to saunas. The open-lung
biopsy, however, showed numerous noncaseating granulo-
mas that were evidently due to a mycobacterial infection.
Some of the granulomas obstructed the lumens of bron-
chioles, which led to “obstructive pneumonitis” mani-
fested by the presence of foamy macrophages in the
alveoli. Undoubtedly, this was the basis of the infiltrate
with the ground-glass appearance, that was seen on the CT
scan.

It has been suggested that small nodules, with and
without bronchiectasis, are a characteristic feature of
MAC pulmonary infections. In fact, reports of this
infection are noteworthy for the variable presentations

![Figure 2. Nonnecrotizing granuloma located in interstitium
away from the bronchioles. The lesion includes several multinu-
There also may be mass densities suggesting a malignant neoplasm, cavitary upper zone disease similar to tuberculosis, and bronchiectasis in which the MAC seems to be a superinfection. The course usually is indolent, although rapid progression may be seen in those with immune suppression, particularly in patients with AIDS, with evidence of disseminated disease. The radiograph, in the latter, may show diffuse or focal changes, but an autopsy study suggests that these may be due to coexisting disease rather than to MAC infection. The variable clinical picture, of course, undoubtedly reflects the patient’s immune status and the nature and location of preexisting conditions, eg, bullae and bronchiectatic changes, which become infected with MAC. Another element in the variability may, however, be the fact that the MAC consists of a number of different serotypes with possible differences in virulence. Thus, isolates in AIDS, most frequently serovars 4 and 8, have been found to be more virulent than other MAC strains.

The presentation in the case reported in this paper is, indeed, more characteristic of that seen in patients with immune suppression: rapid progression, widespread involvement of the lungs, and apparent dissemination to the skin. However, this was not established by a biopsy. On the other hand, there was no evidence for an immune disorder, and it has to be speculated that the patient was infected with a more virulent strain of this organism.

With regard to the origin of the infection, MAC is widely distributed in the environment, but attention has been drawn to water sources. Of interest to this case is the preferential growth of MAC in hospital hot water supplies; presumably residential water supplies could also be affected. Infection could be acquired by inhalation or ingestion, and it has been speculated that showers might be important in transmission. The only direct evidence thus far is provided in a study by von Reyn and coworkers with the use of pulsed-field gel electrophoresis linking M. avium infection in five AIDS patients to infected hot water in two New England hospitals. The chain of transmission was, however, vague, and it is not clear whether patients were infected by drinking, showering, or possibly through endoscopy. In the case presented in this report, there is no doubt that the patient used the hot tub repeatedly, and the close matching on multilocus enzyme electrophoresis and RFLP analysis indicates that this was the source of infection. Differences found in the RFLP patterns are not unusual since M. avium isolates shown to be identical by pulsed-field electrophoresis have been found to differ in up to five copies of IS 1245. The hot tub had air jets at the side creating bubbling through the water, and the patient was aware of a mist over the surface. Parker and coworkers have described a “bubble-burst, jet droplet” mechanism producing aerosols enriched with MAC; this may be of importance in transmitting such infections. The hot tub, perhaps, creates a situation similar to the experimental one.

A final feature of this case is the unusual responsiveness to treatment, with complete clearing of the pulmonary and skin changes and no evidence of relapse after 11 months. MAC infections characteristically show multidrug resistance, particularly when criteria for tuberculosis are used in testing. In the case reported herein, it was possible to treat the patient with four drugs to which there was at least moderate sensitivity, and this undoubtedly played a part in the excellent result obtained.

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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. viridatum*; 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 1A). 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 honeycombing fibrosis (Fig 1B). He never had demonstrable precipitating antibodies to common FL-related antigens (Thermoaclinozymectes, 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).

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

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

**Probable New Antigens, Penicillium brevicompactum and P olivicolor**

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