

Hypersensitivity Pneumonitis Associated With *Mycobacterium avium* Complex and Hot Tub Use

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Many diseases, mainly infectious and inhalational, have been associated with the use of hot tubs. "Hot tub lung" is a recently described disease entity associated with *Mycobacterium avium* complex (MAC) and is thought to be either an infection or a hypersensitivity pneumonitis. We describe 2 patients with progressively worsening respiratory symptoms and pulmonary function, along with diffuse radiographic changes consisting primarily of ground-glass opacities. Treatment with corticosteroids, based on lung biopsies suggesting sarcoidosis in 1 patient and eosinophilic bronchiolitis in the other, resulted in little improvement with both patients experiencing respiratory failure. Both patients continued regular and continued hot tub use despite ongoing respiratory difficulties, and MAC was

identified in the hot tub water and/or lung tissue from each patient. Discontinuation of hot tub use, without antimicrobial therapy, led to prompt improvement in symptoms, pulmonary function, and radiographic abnormalities, strongly supporting a diagnosis of hypersensitivity pneumonitis. Hypersensitivity to MAC, rather than an infection, is the likely underlying mechanism in these 2 cases of hot tub lung.

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FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; MAC = *Mycobacterium avium* complex

Use of hot tubs is growing in popularity in the United States. Many adverse outcomes have been described with the use of hot tubs: burns, *Pseudomonas aeruginosa* folliculitis, inhalational injuries from sanitizing chemicals,¹ "humidifier lung" (hypersensitivity pneumonitis associated with a humidifier and caused by various fungi),² "hot water fever," legionellosis,³ and more recently "hot tub lung."⁴⁻⁶

Hot tub lung is an incompletely characterized disease associated with *Mycobacterium avium* complex (MAC) growing in the hot tub water. It is unclear from previous reports whether this disorder is an infection or hypersensitivity pneumonitis. We report 2 cases of hot tub lung that had clinical and radiographic features consistent with hypersensitivity pneumonitis.

REPORT OF CASES

Case 1

A 45-year-old female exsmoker (25 pack-years; quit in February 2000) presented to our institution in July 2000 for a second opinion regarding a diagnosis of "sarcoidosis." She had a history of rheumatoid arthritis and fibromyalgia

but no lung disease. Her problems began in February 2000 when she developed fever (38.3°C), chills, cough, and dyspnea. Pneumonia was diagnosed, and she was treated with a course of antibiotics, inhaled bronchodilators, and eventually prednisone. She noted marked improvement with prednisone therapy, but her symptoms appeared to worsen when her prednisone dosage was decreased from 60 mg/d to 35 mg/d. Pulmonary function testing showed a total lung capacity of 6.29 (117% of predicted), forced vital capacity (FVC) of 1.96 (53% of predicted), and forced expiratory volume in 1 second (FEV₁) of 1.22 (40% of predicted) with an FEV₁/FVC ratio of 62%, consistent with mild obstruction. Arterial blood gas analysis while the patient was breathing room air showed a Po₂ of 58 mm Hg, Pco₂ of 36 mm Hg, and pH of 7.51. The patient became progressively hypoxemic over 6 months, eventually requiring supplemental oxygen. High-resolution computed tomography (HRCT) of the chest revealed bilateral ground-glass opacities with air trapping on expiration (Figure 1, left). An open lung biopsy disclosed well-formed non-necrotizing granulomas centered on small airways (Figure 2). Cultures and stains for fungi, mycobacteria, and bacteria were negative. The patient had a hot tub installed in her basement in December 1998 and used it 1 to 2 times per day. The water was changed every 4 months. A sample of water from her hot tub revealed MAC and a few colonies of *Alternaria* species; the patient's sputum was negative for these organisms. The hot tub was drained, and the room was closed. Three months later, prednisone and oxygen

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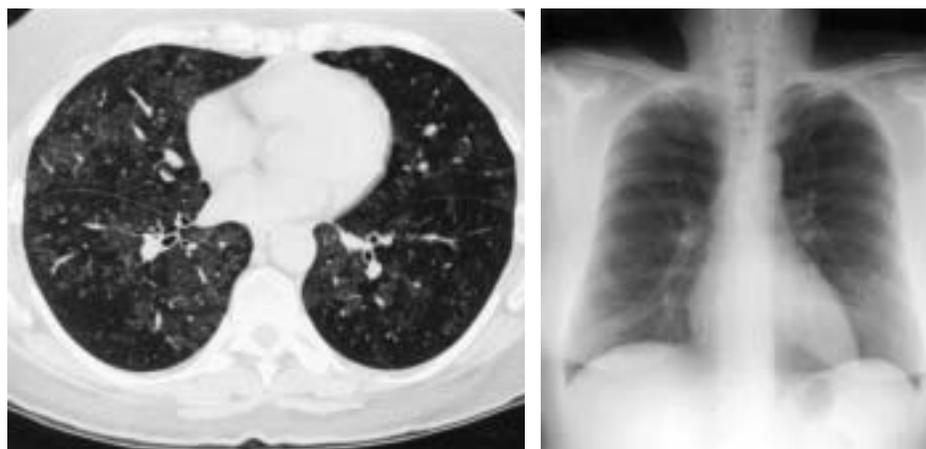


Figure 1. Case 1. Left, High-resolution computed tomography of the chest revealing patchy areas of ground-glass attenuation scattered in both lungs with air trapping on expiration. Right, Chest radiograph is normal 3 months after patient discontinued use of the hot tub.

were discontinued, with improved symptoms and pulmonary function test results as well as a normal chest radiograph (Figure 1, right).

Case 2

A 50-year-old female exsmoker (12 pack-years; quit in 1970) presented to our institution for a second opinion regarding "eosinophilic bronchiolitis." She had been previously healthy, other than undergoing bariatric surgery 21 years previously. In November 1999, cough, rhinorrhea, and mild dyspnea developed in association with ventilator duct cleaning at her workplace. The patient was treated with antibiotics without improvement and with gradual worsening of her symptoms. In March 2000, she had worsening diffuse bilateral alveolar infiltrates on chest radiography and respiratory failure. She was treated with antibiotics and high-dose corticosteroids (dosage unknown), and 2 days later her chest radiograph was normal.

Transbronchial biopsy revealed acute and chronic bronchitis with abundant eosinophils and plasma cells. Prednisone, 80 mg/d, was initiated. The patient continued to require 25 mg of prednisone daily, eventually progressing to supplemental oxygen, and was being evaluated for possible lung transplantation. Pulmonary function testing showed an FVC of 1.66 (49% of predicted), FEV₁ of 1.29 (46% of predicted), and FEV₁/FVC of 82%, consistent with severe restrictive defect. The week before presentation at our institution in January 2001, methotrexate was instituted without recognizable benefit. Physical examination was remarkable for obesity and bibasilar crackles but no clubbing. Chest HRCT revealed bilateral ground-glass attenuation (Figure 3). Arterial blood gas analysis showed a Po₂ of 56 mm Hg, Pco₂ of 35 mm Hg, and pH of 7.44. Transtho-

racic echocardiography revealed normal ventricular size and function, with a right ventricular systolic pressure calculated to be 62 mm Hg. An open lung biopsy revealed extensive, well-formed nonnecrotizing and focally necrotizing granulomatous inflammation with virtually all the granulomas centered on the small airways, with focal intrabronchiolar localization, obliterating the lumens (Figure 4). Grocott methenamine silver and auramine-rhodamine stains were negative for organisms. The patient had a hot tub in her home, and a sample of water revealed MAC. Cultures of her lung biopsy tissue were positive for *Mycobacterium avium-intracellulare* after 8 weeks. Strict avoidance and drainage of the hot tub were advised. One month after the hot tub was drained, the patient's FEV₁ was 2.34 (83% of predicted), chest radiograph was normal, right ventricular systolic pressure was 41 mm Hg (decreased by 21 mm Hg), and she no longer needed supplemental oxygen or prednisone.

DISCUSSION

MAC is commonly found in natural waters and tap water.⁷ It rarely causes disease in the immunocompetent host in whom it has been recognized mainly as a chronic pulmonary infection, often associated with bronchiectasis.⁸ In patients with the acquired immunodeficiency syndrome and other immunosuppressed hosts, disseminated MAC occurs more frequently. Other manifestations of MAC include lymphadenopathy, pulmonary nodules, consolidation, interstitial infiltrates, cavities, and even masslike lesions.⁹

Five other articles have described hot tub-related respiratory illness similar to our case reports. Kahana et al⁴ described a 20-year-old woman presenting with cough and

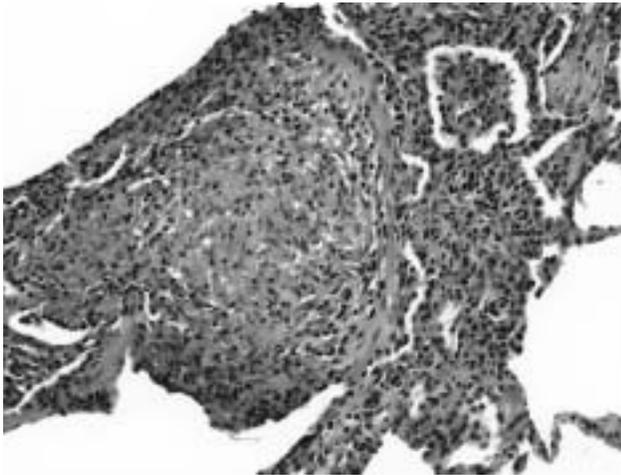


Figure 2. Case 1. Photomicrograph of right lower lung wedge revealing well-formed nonnecrotizing granulomas centered on small airways (hematoxylin-eosin, original magnification $\times 20$).

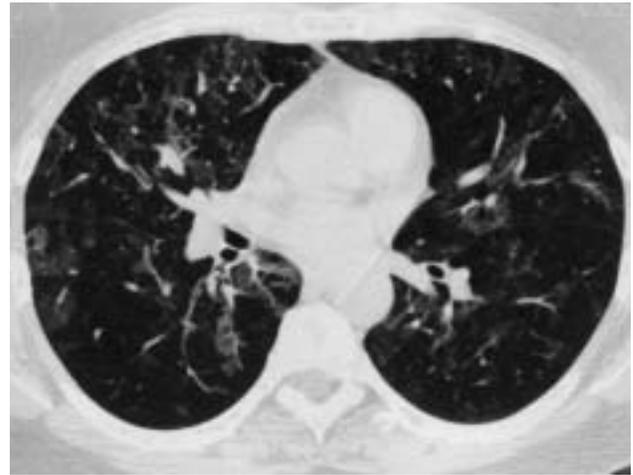


Figure 3. Case 2. High-resolution computed tomography of the chest showing bilateral ground-glass opacities through the central portions of each lung with relative sparing in the periphery.

progressive exertional dyspnea. Chest HRCT revealed diffuse ground-glass infiltrates. Open lung biopsy showed numerous nonnecrotizing granulomas. MAC was isolated from the patient's lung specimen and hot tub water. She had no apparent evidence of immunosuppression or bronchiectasis. The patient was treated with antimycobacterial drugs, and even though the organism was at least moderately resistant to the treatment regimen prescribed, she had complete resolution of her illness in fewer than 3 months. It would be unusual for a true MAC "infection" to resolve this quickly, and assuming that the patient was instructed to discontinue hot tub use, this course of illness would be more consistent with hypersensitivity pneumonitis than with a MAC infection.

Embil et al⁵ reported 5 cases of respiratory illness associated with hot tub use. Chest radiography revealed bilateral interstitial or micronodular infiltrates. Lung biopsy specimens showed "noncaseous" granulomas. MAC was isolated from sputum samples, lung biopsy specimens, and hot tub water samples. All 5 patients recovered after discontinuation of hot tub use and without antimycobacterial therapy. The latter observation supported the authors' interpretation that this respiratory illness represented hypersensitivity pneumonitis rather than infection.

Of 10 patients whose lung biopsy results were reported recently by Khor et al,⁶ 4 improved with corticosteroids, 4 with antimycobacterial drugs, and 2 with combined treatment, suggesting that at least some had features more consistent with hypersensitivity than with infection.

In a recent case series reported by Mangione et al,¹⁰ an entire family was affected. The index case was initially

treated with prednisone only, and improvement was noted. The patient had further improvement while away from her home on vacation. This would be consistent with hypersensitivity rather than infection. Radiographic and pathological findings were similar to our cases. Ultimately, the entire family received antimycobacterial treatment, and in 6 months complete clinical and radiographic resolution was noted. It would be highly unusual for a typically tenacious and resistant MAC "infection" to resolve so quickly. Assuming that the family no longer used the hot tub, the clinical course is more consistent with hypersensitivity pneumonitis.

There have been few other reports of mycobacteria causing hypersensitivity pneumonitis. Outbreaks of hypersensitivity pneumonitis have occurred in metalworking facilities caused by *Mycobacterium* species growing in contaminated metal removal fluids.¹¹⁻¹³ Surveys of metalworking facilities have correlated mycobacterial contamination of metal removal fluids with increased risk of hypersensitivity pneumonitis.¹² In these work settings, contaminated fluids can easily become aerosolized and inhaled.

In our 2 patients, the severe respiratory symptoms, radiographic infiltrates, and hypoxemia improved with corticosteroid therapy and discontinuation of hot tub use. Note that corticosteroids alone had proved insufficient until avoidance measures were instituted. In the absence of a specific diagnostic test, improvement with discontinuation of hot tub use and institution of corticosteroid therapy, without recourse to additional antimycobacterial treatment, argue compellingly for a hypersensitivity phenomenon rather than an infection. In addition, the features seen on

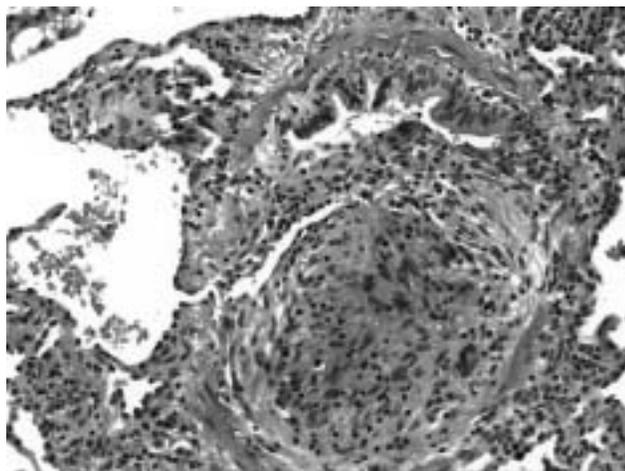


Figure 4. Case 2. Photomicrograph of right middle lobe wedge excision revealing a well-formed nonnecrotizing granuloma centered on a small airway (hematoxylin-eosin, original magnification $\times 20$).

HRCT, ie, ground-glass opacities and micronodules, are similar to those seen in other cases of hypersensitivity pneumonitis.^{14,15}

Histologically, both of these cases showed changes that are essentially a “hybrid” of those seen in hypersensitivity pneumonitis and those of a granulomatous infection of the lung. Both cases demonstrated well-formed, predominantly nonnecrotizing bronchiolocentric granulomas. Case 2 also had a patchy chronic interstitial pneumonia and a cellular chronic bronchiolitis along with rare granulomas and focal necrotizing change centrally in the granulomas.

The “typical” and most characteristic features of hypersensitivity pneumonitis are chronic bronchiolitis and chronic interstitial pneumonia with bronchiolocentric accentuation. The presence of small, poorly formed or “vague” granulomas or occasional scattered giant cells is also common. Bronchiolitis obliterans with organizing pneumonia–like foci are also frequently seen. These changes are in contrast to the pattern of granulomatous inflammation seen in most reported cases of hot tub lung, including the present 2 cases. In these cases, the granulomas were distinct and well formed. While also being centered on the small airways, these areas of granulomatous inflammation typically are more florid, may have central necrotizing changes, and are histologically more suggestive of an infectious process than hypersensitivity pneumonitis or sarcoidosis (which typically has a lymphangitic rather than a pure bronchiolocentric distribution). Thus, in many respects, it is the histopathology in hot tub lung that has been the most suggestive finding to support the “infec-

tious” etiology theory. The histopathology and the organisms grown in lung tissue cultures and seen on special stains of lung granulomas are distinctly unusual features of hypersensitivity pneumonitis because in hypersensitivity pneumonitis both cultures and special stains are expected to be negative for organisms.

Hot tubs provide an excellent growth environment for MAC; the warm temperature promotes growth,¹⁶ and owners frequently do not clean them or change filters as often as recommended. At temperatures higher than 84°F, chlorine loses much of its disinfectant properties.¹⁷ Isolates of *M avium-intracellulare* complex are variably susceptible to chlorine, with the slower growing strains tending to be more resistant to chlorine.¹⁸ The steam and bubbles generated efficiently aerosolize the organism,¹⁹ facilitating easy inhalation.

Mycobacteria have acid-rich cell walls that are highly antigenic. Elevated levels of IgG antibody directed at mycobacteria may be detected in hypersensitivity pneumonitis caused by these species.¹² Alternatively, mycobacteria may not be the direct causative antigen but acts as an adjuvant that enhances hypersensitivity reaction to other environmental antigens. Muramyl dipeptide, a component of mycobacteria, has been used as an adjuvant in producing animal models of hypersensitivity pneumonitis.²⁰ Molina et al²¹ reported 1 case of hypersensitivity pneumonitis after vesicular bacille Calmette-Guérin vaccine for treatment of superficial bladder cancer.

CONCLUSION

Our 2 patients had many features of hypersensitivity pneumonitis, including ground-glass infiltrates, clinical improvement with corticosteroids, and resolution of symptoms with discontinuation of hot tub use. Neither patient received antimicrobial therapy appropriate for MAC; in fact, both improved with immunosuppression. Of note, all the cases of hot tub lung reported in the literature have been associated with a hot tub indoors at a personal residence. Although hot tub lung often demonstrates MAC on culture and special stains with a histologic pattern of involvement that is more suggestive of an infectious etiology, the clinical and radiographic features, particularly the usual complete response to corticosteroids and discontinuation of hot tub use, as well as the lack of need for antimycobacterial treatment, support a diagnosis of hypersensitivity pneumonitis.

An estimated 340,000 new hot tubs were sold in the United States in 1998, and it is highly likely that this number has increased. We recommend that physicians maintain a high index of suspicion for hot tub lung and include questions about hot tub use in their routine review of symptoms in patients with respiratory problems.

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