Diffuse Pulmonary Disease Caused by Nontuberculous Mycobacteria in Immunocompetent People (Hot Tub Lung)

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Abstract

The clinicopathologic spectrum of infections due to nontuberculous mycobacteria (NTM) includes cavitary disease, opportunistic infection, and nodular disease associated with bronchiectasis. We report a less well-described manifestation of NTM infection: 10 immunocompetent patients without preexisting bronchiectasis had radiographic evidence of diffuse infiltrative lung disease. The most common symptoms were dyspnea, cough, hypoxia, and fever. All 10 patients had used a hot tub. Histologic examination revealed exuberant nonnecrotizing, frequently bronchiolocentric, granulomatous inflammation in all cases. In 1 case, necrotizing granulomas were also noted. The inflammation often was associated with patchy chronic interstitial pneumonia and organization. Cultures revealed NTM in all cases (Mycobacterium avium complex in all but 1 case), but staining for acid-fast bacilli was positive in only 1 case. Four patients received corticosteroids alone for presumed hypersensitivity pneumonia, 4 were treated with antimycobacterial therapy, and 2 received both. All patients demonstrated significant improvement at the time of follow-up. These findings suggest that disease due to NTM may manifest as diffuse infiltrates in immunocompetent adults and that hot tub use may be an important risk factor for this disease pattern.

A number of pulmonary diseases are associated with nontuberculous mycobacteria (NTM), particularly *Mycobacterium avium* complex (MAC). The best known include mimics of classic cavitary tuberculosis, opportunistic infections in immunocompromised people (particularly MAC in people with AIDS), and patchy nodular disease associated with bronchiectasis.[1] In the latter group, the assumption has been made that bronchiectasis predisposes to colonization and low-grade infection by atypical mycobacteria, although that scenario has been questioned by studies suggesting that the atypical mycobacterial infection actually may precede and *cause* the bronchiectasis.[2,3]

A less well-recognized clinicopathologic manifestation of MAC infection also has been reported: diffuse lung disease—not associated with bronchiectasis—in otherwise healthy people.[4-6] Some cases have been linked to hot tub exposures,[5,6] and 1 report suggested that these cases represent a form of hypersensitivity pneumonia (extrinsic allergic alveolitis) rather than an infection.[5] Clinically, radiologically, and pathologically, noninfectious diseases such as hypersensitivity pneumonia and sarcoidosis have been considered in the differential diagnosis in these cases.

Herein we report our experience with 10 cases of diffuse infiltrative pulmonary disease caused by atypical mycobacteria, primarily MAC, in otherwise healthy people.

Materials and Methods

We searched our consultation files for culture-confirmed cases (during the period January 1, 1990-December 30, 1998) of nontuberculous mycobacterial infection causing diffuse lung disease in otherwise healthy people who lacked predisposing

factors for the development of mycobacterial infection, in particular immunosuppression and bronchiectasis. Clinical, radiologic, and follow-up information was obtained from the patients and their physicians. A history of hot tub use was not a criterion for selection, but information about hot tub exposure was sought specifically at follow-up. An open lung biopsy specimen was available for histologic evaluation in all but 1 case, in which a transbronchial biopsy specimen was available. Histologic sections stained with H&E as well as special stains for acid-fast bacilli and fungal organisms were reviewed for each case.

Results

Clinical Findings

We identified 10 cases; 4 were men, and 6 were women. Their ages ranged from 29 to 68 years (mean, 50 years). The clinical findings are summarized in ▮Table 1▮. All 10 patients had a history of hot tub exposure. Three patients continued to use their hot tubs after diagnosis and treatment of their

disease, but they kept the water clean. The remaining 7 patients denied continued hot tub use. Chest radiographs in all cases revealed a diffuse infiltrative pattern. Computed tomography scans (6 cases) showed patchy ground-glass change. In 3 cases, the infiltrates were more prominent in the lower lobes. Culture revealed MAC in all but 1 case. In 1 case, *Mycobacterium fortuitum*, *Nocardia, Pseudomonas,* and *Candida* organisms were also cultured. In 1 case, NTM were cultured, but species were not identified. Four patients were treated with antimycobacterial therapy, 4 patients received oral corticosteroids for presumed hypersensitivity pneumonia, and 2 patients received both antimycobacterial therapy and oral corticosteroids. The patients were followed up for 1 to 10 years (mean, 3.4 years). All patients experienced substantial improvement in clinical and radiologic findings at the time of follow-up.

Case 2 deserves further mention. After an initial diagnosis of sarcoidosis, high-dose corticosteroid treatment was initiated. Two months later, lung cultures became positive for MAC, and she was still dyspneic and febrile. Multiple sputum and blood cultures taken at this time subsequently were

▮Table 1▮
Clinical Findings in 10 Cases of Nontuberculous Mycobacterial Infection

Case No./ Sex/Age (y)	Hot Tub Exposure	Signs and Symptoms	Radiographic Findings	CT Findings	Treatment	Follow-up
1/M/68	Yes	Severe cough, dyspnea, fever	Diffuse interstitial infiltrates	ND	Oral corticosteroids	1 y; marked improvement, but still experiences dyspnea
2/F/29	Yes	Chest pain, dyspnea, fatigue, hypoxia	Diffuse, finely nodular interstitial infiltrates	Diffuse ground-glass opacities	Oral corticosteroids, antimycobacterial therapy (after positive cultures)	10 y; negative chest radiograph; asymptomatic except for occasional wheeze with irritants
3/M/67	Yes	Dyspnea, profound hypoxia	Lower lobe predominant interstitial infiltrates	ND	Oral corticosteroids	6 y; improvement, but still experiences dyspnea
4/F/51	Yes	Cough, dyspnea, fatigue, fever, malaise	Diffuse interstitial infiltrates	Hazy alveolar infiltrates	Antimycobacterial therapy	4 y; improved symptoms, negative CT results
5/F/45	Yes	Cough, dyspnea, fever, hypoxia	Diffuse reticulonodular pattern	Nonspecific alveolitis	Oral corticosteroids	3 y; marked improvement
6/M/57	Yes	Worsening cough, dyspnea	Diffuse haziness	Lower lobe predominant ground-glass opacities	Antimycobacterial therapy	4 y; no symptoms, negative CT results
7/F/61	Yes	Cough, dyspnea, fever, hypoxia	Diffuse interstitial infiltrates	"Compatible with hypersensitivity pneumonia"	Antimycobacterial therapy	1 y; no symptoms
8/F/61	Yes	Dyspnea, hypoxia	Diffuse interstitial infiltrates	Patchy ground-glass opacities	Antimycobacterial therapy	2 y; no symptoms, negative chest radiograph
9/F/29	Yes	Cough, dyspnea	Bilateral "pneumonia"	ND	Oral corticosteroids (short course, followed by antimycobacterial therapy)	2 y; no symptoms, negative chest radiograph
10/M/31	Yes	Cough, dyspnea, hypoxia	Lower lobe predominant interstitial infiltrates	ND	Oral corticosteroids	1 y; no symptoms

CT, computed tomography; ND, not done.

positive for MAC. Corticosteroid treatment was discontinued, and 4-drug antimycobacterial therapy was started. During the next 3 months, radiographs cleared, she became asymptomatic, and all cultures became negative. She is well 10 years later.

Pathologic Findings

The main histologic features are listed in ❚Table 2❚. Nonnecrotizing granulomatous inflammation was present in

❚Table 2❚
Histologic Findings in 10 Cases of Nontuberculous Mycobacterial Infection

| Histologic Finding	No. of Cases
Nonnecrotizing granuloma	10
Necrotizing granuloma	1
Organizing pneumonia	4
Patchy chronic interstitial pneumonia	10
Cellular bronchiolitis	2

all 10 cases ❚Image 1A❚ and ❚Image 1B❚. In addition, a single biopsy specimen also exhibited occasional necrotizing granulomas ❚Image 1C❚. The granulomas tended to be solitary with a cuff of lymphocytes and were located within the airspaces, the bronchiolar lumens, and the interstitium ❚Image 2❚. Organizing pneumonia with air space–filling fibroblastic plugs was noted in 4 cases ❚Image 3❚. Both the granulomas and the organization showed a tendency for a centrilobular distribution. Pleural or septal involvement was not present. Patchy chronic interstitial pneumonia with alveolar septal thickening due to chronic inflammatory infiltrate was present in all cases, but was prominent in 4 cases (Image 3). Special stains for acid-fast bacilli were positive in only 1 case.

Discussion

Diseases due to NTM do not require notification of public health authorities in the United States, and, therefore,
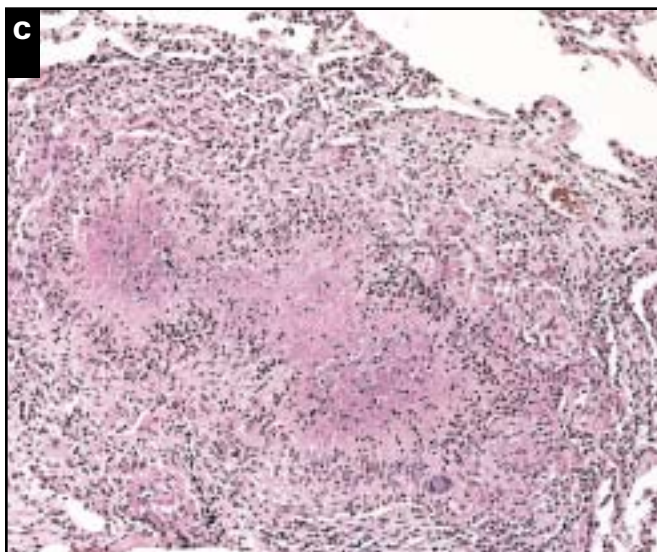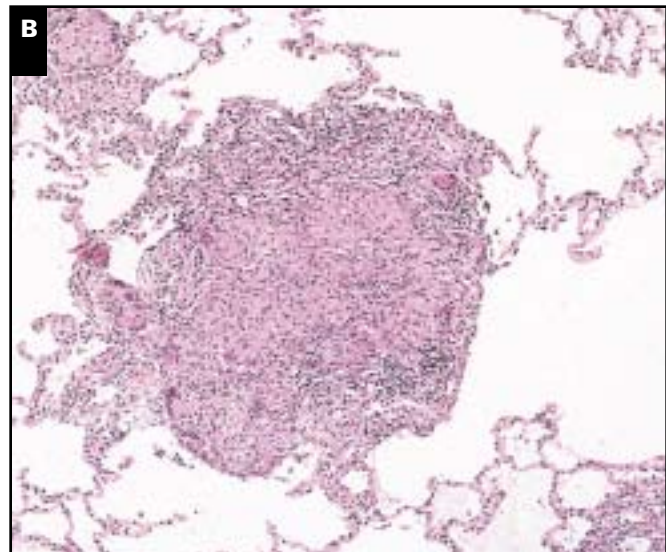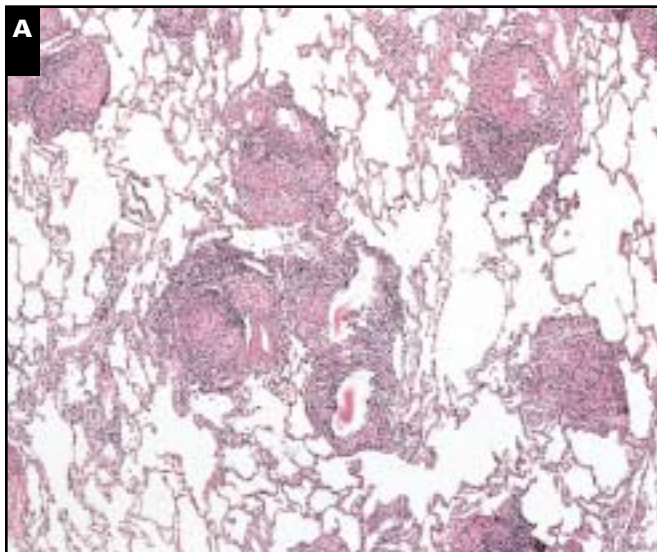
❚Image 1❚ *Mycobacterium avium* complex causing diffuse lung disease. **A**, Scanning power microscopy shows scattered discrete granulomas with relatively normal intervening lung parenchyma. **B**, The granulomas have a moderate cuff of chronic inflammation and the adjacent alveoli are normal. **C**, Necrotizing granulomas were identified in only 1 of 10 cases. (H&E)
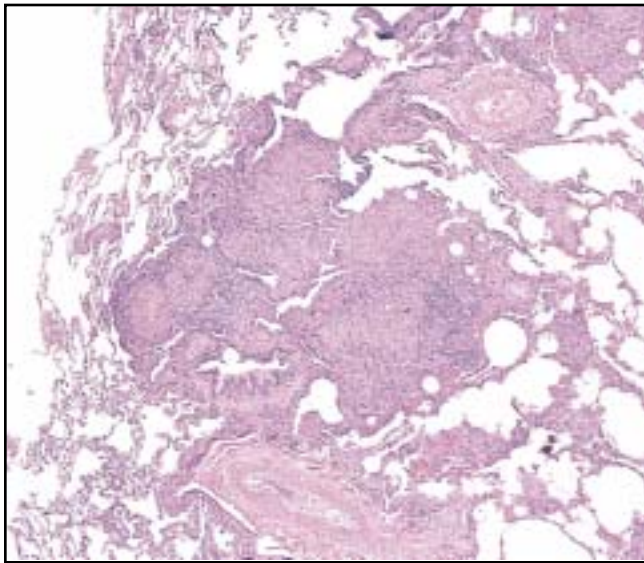
Image 2 *Mycobacterium avium* complex causing diffuse lung disease. Some cases showed bronchiolocentric distribution of the granulomas. In this region, there was some tendency to coalescence of granulomas but less than that seen in sarcoidosis. The inflammatory cuff of the granulomas shown here is greater than that associated with sarcoidosis (H&E).
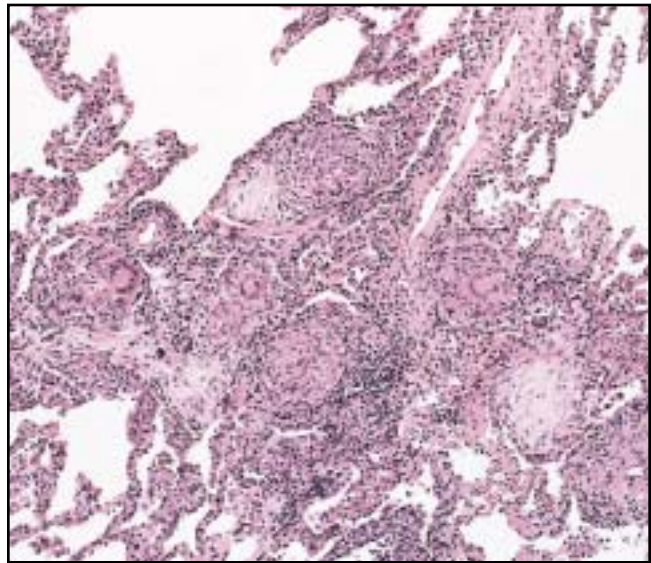
Image 3 *Mycobacterium avium* complex causing diffuse lung disease. Some cases had organizing pneumonia associated with the granulomas. A patchy chronic interstitial pneumonia is also prominent in this case (H&E).

reliable estimates of their incidence or prevalence are limited. In 1 study, based on 1979-1980 state laboratory reports, NTM constituted approximately one third of the 32,000 mycobacterial isolates.[7] A 1991-1992 Centers for Disease Control and Prevention study, which included results from 33 state laboratories, demonstrated a dramatic increase in the prevalence of NTM.[8] Despite the increase in isolates of *Mycobacterium tuberculosis* noted in the United States since 1985, there are now more isolates of MAC than of *M tuberculosis,* with the latter representing only 26% of the total mycobacterial isolates.[8] The reasons for this dramatic increase in NTM infection are unknown, but better clinical recognition and more widespread culturing for pulmonary and disseminated disease may have important roles, as may the increased use of heated water in activities of daily living.[9]

MAC, followed by *Mycobacterium kansasii*, is the most frequent NTM causing lung disease in the United States. In our study, MAC was found in all 9 cases in which the species of the NTM were identified. Clinicopathologic patterns of MAC infection include cavitary disease, opportunistic infection in immunocompromised patients, nodular infiltrates associated with bronchiectasis, and diffuse interstitial lung disease **Table 3**. Eosinophilic pneumonia has been reported rarely.[10] Similar to tuberculosis, NTM infection may manifest as cavitary disease. However, patients with cavitary disease due to NTM are epidemiologically distinct from patients with tuberculosis: they are older, more commonly

white, and have underlying pulmonary disorders such as chronic obstructive pulmonary disease, previous tuberculosis, usual interstitial pneumonia, malignant neoplasm, cystic fibrosis, or pectus excavatum or have undergone chest surgery.[11-16] Radiographs reveal that cavitary disease due to NTM resembles cavitary disease due to tuberculosis. However, NTM tend to cause thin-walled cavities with less surrounding parenchymal consolidation and more pleural involvement than tuberculosis.[8]

HIV-infected patients are at high risk of developing disease due to NTM, especially MAC,[17] and disseminated MAC is the most common bacterial infection in patients with AIDS.[18,19] However, pulmonary disease occurs in only 2.5% of disseminated MAC cases.[20] Localized pulmonary disease due to MAC without evidence of dissemination develops in a similar percentage of MAC-infected AIDS patients.[20,21] Radiographic patterns of pulmonary MAC disease in AIDS

Table 3
Clinicopathologic Patterns of MAC Infection

Clinicopathologic Pattern	Predisposing Factors
Cavitary disease	Chronic pulmonary disorders
Opportunistic infection	AIDS
Small nodular infiltrates with bronchiectasis	Elderly women
Diffuse interstitial infiltrates	Hot tub exposure

MAC, *Mycobacterium avium* complex.

include consolidation or nodular infiltrates and cavitation. The histopathologic characteristics include histiocytic or granulomatous inflammation often associated with necrosis. Numerous organisms usually can be identified by using special stains.

Pulmonary disease caused by MAC also can affect people without obvious predisposing pulmonary disorders or immunocompromise.[1] Many of these people are elderly women who have clusters of small nodules in dependent portions of the lingula or the middle lobe. Reich and Johnson[22] offered the hypothesis that habitual voluntary suppression of cough may lead to the development of nonspecific inflammatory processes in these poorly draining lung regions, on which MAC engrafts.[22] They have proposed the term *Lady Windermere syndrome* to describe this pattern among elderly women and to suggest that their fastidiousness may be its root cause.[22] Studies with high-resolution computed tomography have shown that up to 90% of immunocompetent patients with noncavitary disease due to MAC have associated multifocal bronchiectasis.[23-26] Recent studies have suggested that the MAC infection actually may precede bronchiectasis and be its cause.[2,3] This theory is further supported by the data of Yamazaki et al,[27] who found increased counts of activated CD4+ lymphocytes and neutrophils and elevated concentrations of proinflammatory cytokines and neutrophil elastase in the bronchoalveolar lavage fluid from patients with MAC infection. These cellular and humoral factors may have a role in the development of bronchiectasis in MAC infection.

In the present study, we analyzed 10 cases of diffuse interstitial lung disease caused by NTM in otherwise healthy people. This seems to be a rare (or more likely underrecognized) manifestation of NTM disease, which has been reported infrequently.[4-6,28] Marchevsky et al[4] described 7 patients with radiographic evidence of bilateral, diffuse interstitial infiltration. Three of these patients had underlying malignant neoplasms treated with chemotherapy, and 1 had arthritis. The other 3 patients had no underlying disorders. MAC or *Mycobacterium gordonae* were isolated from the lung tissue, which histologically showed interstitial fibrosis and organizing pneumonia; nonnecrotizing granulomas were found in only 1 case. In contrast, all of our cases exhibited granulomatous inflammation. The presence of granulomatous inflammation in our cases suggests that MAC had an important role in the disease process. As a matter of fact, biopsy-proven granulomatous inflammation together with NTM-positive cultures in a symptomatic patient meets the American Thoracic Society's diagnostic criteria for nontuberculous mycobacterial lung disease.[8]

In our study, all patients had a history of hot tub exposure. The association with hot tub use is remarkable: the criteria for the selection of cases for this study were the presence of diffuse lung disease–associated NTM in otherwise healthy patients. Interestingly, all 10 patients who fit these criteria had hot tub exposure, which was discovered at the time they were contacted for follow-up.

Extensive environmental studies in the United States have shown that MAC grows well in natural waters.[29] It also has been shown that the growth of MAC is favored by hot water.[30] MAC strains are preferentially aerosolized, providing a possible mechanism for airborne acquisition of these organisms.[9] Powerful jets of air or water in hot tubs further promote aerosol formation. These data, together with our observations, suggest that conditions of hot tub water favor the growth and transmission of MAC, and proper disinfecting of hot tubs is probably necessary to prevent such infections.

MAC-related pulmonary disease has been described in patients with exposure to hot tub water contaminated with MAC.[5,6,28] Whether this should be regarded as a transient infection or a hypersensitivity response to MAC is controversial.[5,6,28,31-33] Kahana et al[6] reported a case of 1 patient who had rapidly progressive disease, widespread involvement of both lungs, and apparent dissemination to the skin. There was no evidence of an immune disorder. The clinical features suggested an infectious process, perhaps due to a more virulent strain of MAC. However, the infection proved to be exceptionally responsive to treatment, and there was complete resolution of the disease with a 4-drug regimen of antituberculous agents. Embil et al[5] reported 5 cases of respiratory illness in healthy subjects using hot tubs contaminated with MAC. The short time between the exacerbation of the symptoms and the hot tub exposure and the spontaneous recovery of all patients with cessation of the hot tub use favored a hypersensitivity reaction. However, no serologic proof of an immunologic reaction to MAC or the hot tub water has been obtained.

The most common histopathologic finding in our study was the presence of nonnecrotizing granulomas. The differential diagnostic possibilities for this type of lesion include sarcoidosis, hypersensitivity pneumonia, and other diffuse granulomatous infections. In sarcoidosis, coalescing nonnecrotizing granulomas are distributed along the lymphatic channels, involving the pleura, interlobular septa, and bronchovascular bundles ❚Image 4❚. The granulomas are composed of tightly clustered epithelioid histiocytes and occasional multinucleated giant cells with few intervening lymphocytes or other inflammatory cells.[33] The lesions are well circumscribed and often surrounded by only a thin rim of chronic inflammatory cells. In addition, the granulomas often are coalescent and associated with hyalinization. Marked interstitial pneumonia extending into the adjacent pulmonary parenchyma usually is not observed. In the present cases, the granulomas were randomly distributed or
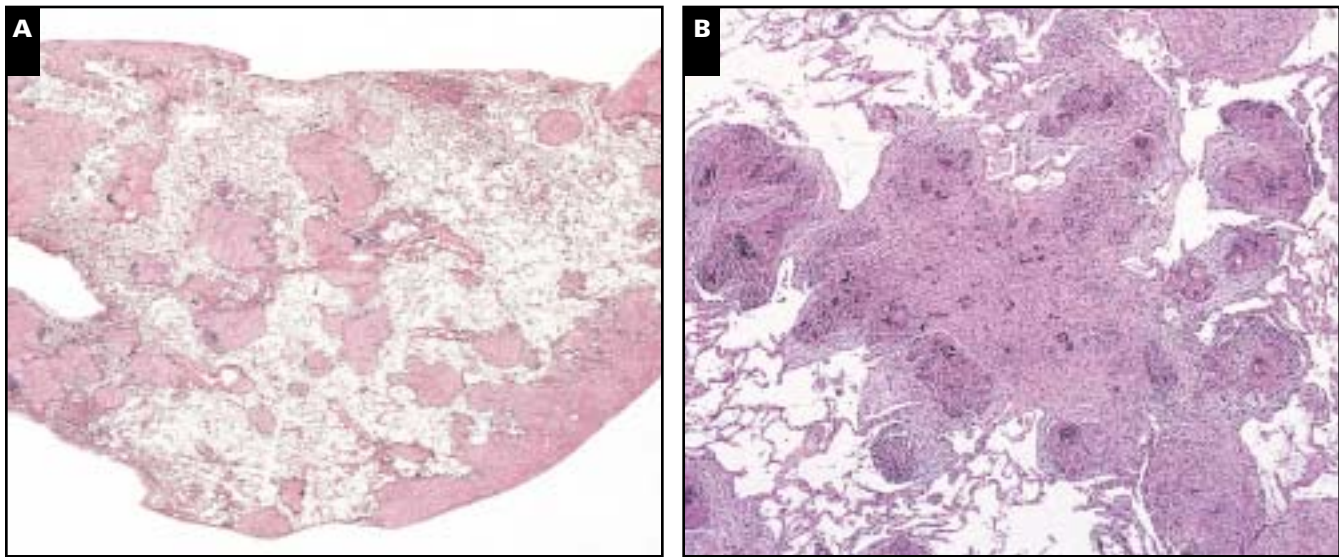
◼Image 4◼ Sarcoidosis. **A** and **B**, The granulomas in sarcoidosis tend to be coalescent and distributed along the lymphatic routes in the pleural septa and bronchovascular bundles. They have an eosinophilic character at scanning power magnification because of the presence of collagen and lack of chronic inflammation. The intervening lung tissue appears unremarkable (H&E).

bronchiolocentric, the cuff of inflammatory cells around the granulomas was prominent, the granulomas did not tend to coalesce, and associated chronic interstitial pneumonia frequently was present.

Hypersensitivity pneumonia is characterized by the histologic triad of cellular bronchiolitis, patchy chronic interstitial pneumonia, and scattered small granulomas **◼Image 5◼**. The interstitial infiltrate usually overshadows the granulomas. The granulomas are loosely formed, poorly circumscribed, and relatively inconspicuous. They contain a mixture of epithelioid histiocytes, multinucleated giant cells, and lymphocytes. Bronchiolitis obliterans organizing pneumonia–like foci also are often present. In the present study of diffuse pulmonary NTM infection, the granulomas were more prominent than in hypersensitivity pneumonia, and the granulomas tended to overshadow the interstitial inflammation, although some cases had bronchiolitis obliterans organizing pneumonia–like foci. In addition, the granulomas were more exuberant and well formed than seen in typical cases of hypersensitivity pneumonitis.
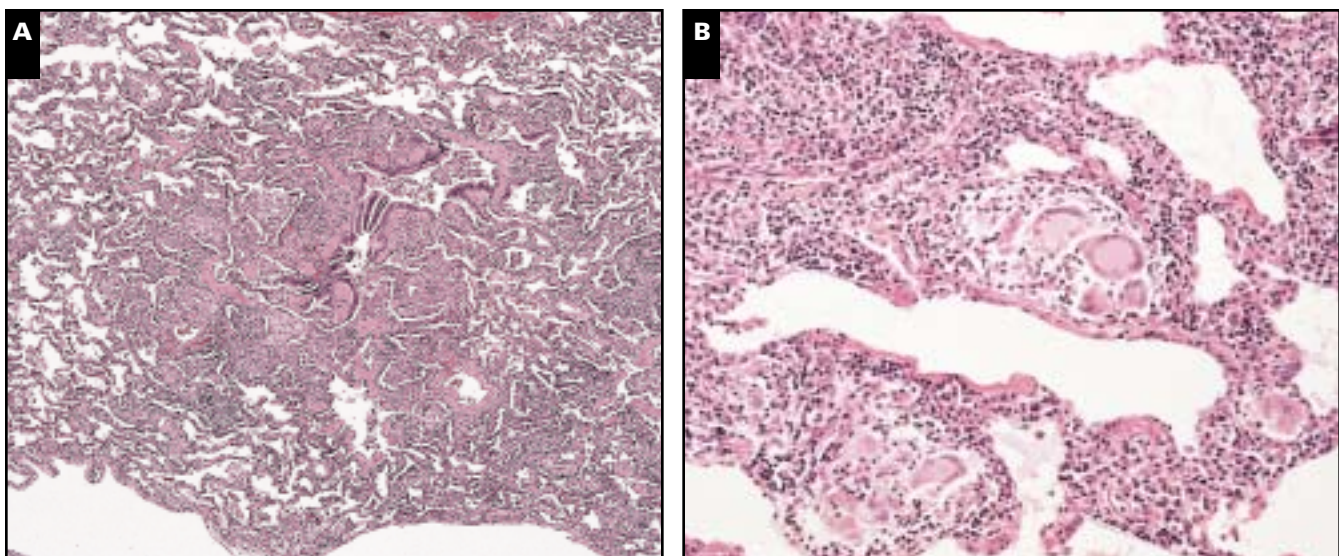
◼Image 5◼ Hypersensitivity pneumonitis. **A** and **B**, The inflammation overshadows granulomas. **A**, The inflammation tends to show a distinct centrilobular accentuation. The granulomas tend to be loose clusters of epithelioid histiocytes and giant cells. **B**, The granulomas are smaller and less well organized than in sarcoidosis or diffuse *Mycobacterium avium* complex. (H&E)

Although it is always necessary to perform special stains for organisms in cases of granulomatous pneumonitis, special stains in our cases of NTM disease only rarely revealed acid-fast bacilli. This emphasizes the difficulties in establishing a tissue diagnosis of diffuse NTM disease associated with hot tub exposure. Cultures of sputum, lung biopsy specimens, and hot tub water, therefore, may be critical to establishing the diagnosis. Based on the rather surprising unanticipated historic data obtained by further questioning of the patients in the present study, it seems as though this association is frequently unrecognized. Therefore, pathologists should have a high index of suspicion for this disease in patients with granulomatous pneumonitis of the type described herein.

A clinicopathologic syndrome caused by MAC that occurs in previously healthy people without underlying immune compromise or lung disease but with exposure to a standing heated water source is described, expanding the spectrum of lung disease secondary to MAC. Although the histopathologic features are distinct from hypersensitivity pneumonia, the pathogenesis of "hot tub lung" may involve infection, hypersensitivity, or both.

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