Editorial

Advances in the Diagnosis and Therapy of Mycobacterial Disease

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In this month's issue of *Cutis*®, Johnson et al[1] remind us of the importance of mycobacterial skin infections. Mycobacterial diseases have reemerged as important skin infections, and tuberculosis has increasing relevance for the dermatologist in the age of biologic therapy for inflammatory skin disease. Reactivation of tuberculosis should be considered a risk with all tumor necrosis factor (TNF) agents, though most reports are related to infliximab.[2] Miliary tuberculosis has been reported in this setting.[3] Reactivation has occurred even in the face of antibiotic prophylaxis.[4] Nontuberculous mycobacterial disease also has been associated with anti-TNF therapy.[5]

Mycobacterial infections are increasing in number worldwide. Factors contributing to the reemergence of tuberculosis in the United States include a global increase in developing countries, an increase in the number of patients with human immunodeficiency virus (HIV) infection, and the emergence of multidrug-resistant tuberculosis.[6] *Mycobacterium bovis* is the causative agent of bovine tuberculosis and the importance of reservoirs in wild animal populations recently has been established.[7] Although *Mycobacterium tuberculosis* accounts for most infections, recent outbreaks of human tuberculosis in the United States also have been related to M *bovis*, and soft cheeses of Mexican origin have been implicated as a source of these infections.[8]

Mycobacterium marinum infection typically occurs with sporotrichoid nodules on an extremity after exposure to water from a fish tank, swimming pool, or brackish inlet. M *marinum* tenosynovitis can mimic arthritic disease. Patients may develop extensive infection after steroid injections. Findings suggestive of M *marinum* tenosynovitis include a fish- or water-associated injury, negative routine bacterial tissue cultures, and poor response to conventional antibiotic treatment.[9]

Mycobacterium fortuitum, *Mycobacterium chelonae*, and *Mycobacterium abscessus* are the rapid growing group of atypical mycobacteria. Patients with M *chelonae* or M *abscessus* tend to be older, more likely to be on immunosuppressive medications, and present with multiple lesions. M *fortuitum* is more likely to manifest as a solitary lesion, and patients are more likely to have had a prior invasive surgical procedure at the infected site.[10] Deep and extensive M *fortuitum* complex infections have been related to nail salon footbaths[11]; M *abscessus* infections have been related to acupuncture treatments[12]; and M *chelonae* infection has followed liposculpture and lipofilling procedures.[13]

Mycobacterium ulcerans infections generally occur in Africa, but cases also have been reported in Mexico.[14] Lupus vulgaris is no longer common but still occurs worldwide.

Although the typical histology of atypical mycobacterial infection is that of granulomatous dermatitis with stellate abscesses and sinus tracts, lichenoid and granulomatous dermatitis has been noted in *Mycobacterium kansasii* and M *marinum* infections.[15] A Fite stain should be prompted by clinical features suspicious for atypical mycobacterial infection, even in the absence of deep granulomatous infiltrates with neutrophilic abscesses.

The diagnosis of mycobacterial disease has been dependent on identifying the organism in smears or culture. DNA hybridization on nitrocellulose strips has been used to identify M *tuberculosis* complex isolates to the species level and compares favorably with polymerase chain reaction (PCR) techniques, biochemical tests, and susceptibility testing.[16] A whole-blood interferon-γ enzyme-linked immunosorbent assay (QuantiFERON TB-2G [QFT-TB]; Cellestis) has demonstrated promise in distinguishing between active tuberculosis and nontuberculous mycobacteriosis. This type of in vitro testing can be used as a supplement to tuberculin skin testing.[17] Conventional and real-time PCR assays for detection of *Mycobacterium leprae* DNA based on the antigen 85B-coding gene or the 85A-C intergenic region can result in detection rates of 100% in patients with multibacillary disease and from 62.5% to 79.2% among those with paucibacillary disease.[18] PCR assays may be negative when mycobacteria are

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not visible in Fite-stained sections. Gene probes that target 16S ribosomal RNA and 16S ribosomal DNA have proved useful in the diagnosis of smear negative mycobacterial disease.[19] Interferon γ release assays using tuberculosis-specific antigens have a sensitivity of 81% in HIV-infected tuberculosis patients.[20] This sort of assay may be useful in the setting of immunosuppression related to biologic therapy for psoriasis where skin testing is less reliable. Elevated levels of soluble urokinase receptor in serum may be a marker for persistent extrapulmonary mycobacterial infection during therapy.[21]

Skin testing has proved useful in the screening for nontuberculous mycobacterial infection in children. In a study of 180 children with chronic cervicofacial lymphadenitis, skin testing was done using antigens of M *tuberculosis*, *Mycobacterium avium*, M *kansasii*, and *Mycobacterium scrofulaceum*. These results compared identification by culture, PCR, or both. One hundred twelve nontuberculous mycobacterial infections were identified (83 caused by M *avium*, 21 by *Mycobacterium haemophilum*, and 8 by other species). Using a 5-mm cutoff for a positive skin test, tuberculin skin testing demonstrated a sensitivity and specificity of 70% and 98%, respectively. *M avium* sensitin, the best-performing skin test, had positive and negative predictive values of 98% and 90%, respectively.[22] It should be noted that a response to therapy may be the ultimate indication of tuberculous skin infection in patients with negative PCR, skin tests, and culture.[23]

Minocycline, doxycycline, clarithromycin, or a combination of rifampicin and ethambutol hydrochloride may be used as initial empiric therapy for M *marinum* infections.[24] Minocycline has been reported as successful even when a patient did not respond to doxycycline.[25]

Deep M *marinum* infections involving the hand can be aggressive and result in permanent disability. Specialists in infectious disease and hand surgery should be consulted.[26] Photodynamic therapy may have some role in the treatment of M *marinum* infections, though more data are needed.[27]

Fluoroquinolones are relatively recent additions to the armamentarium against mycobacterial pathogens. Minimal inhibitory concentrations are not always predictive of clinical response, and lack of intracellular killing may contribute to lower in vivo activity of ciprofloxacin hydrochloride.[28] Clarithromycin or azithromycin are preferred as initial therapy for M *abscessus* but should be supplemented with other drugs such as amikacin sulfate to avoid emergence of resistance.[29]

As mycobacterial disease becomes more common and we use more biologic agents that predispose to mycobacterial infection, dermatologists would do well to remain familiar with the current diagnostic and therapeutic options.

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