Successful Treatment of Disseminated Mycobacterium szulgai Infection with Ciprofloxacin, Rifampicin, and Ethambutol

Sir.

Mycobacterium szulgai, a slow-growing scotochromogenic mycobacterium, was first described by Marks et al. in 1972. Unlike other scotochromogenic mycobacteria, clinical isolates of M. szulgai are usually pathogenic rather than contaminants. Most cases are chronic pulmonary infections, although localized bone and soft tissue infections have also been described. Disseminated M. szulgai infection is extremely rare. Gur et al. reported the only case of disseminated M. szulgai disease with multi-focal osteomyelitis in the literature. Treatment with conventional antituberculous agents was not effective. We report a case with similar clinical manifestations. However, the patient was successfully treated with combination therapy containing ciprofloxacin, which had been reported to be effective for M. szulgai in vitro.

A previously healthy 59-year-old man developed multiple cervical lymphadenopathy in December 1993. Episodic fever with chills was noticed in the following months, and the neck lymph nodes (LNs) continued to enlarge slowly. An initial biopsy suggested angioimmunoblastic lymphadenopathy (AILD). A second biopsy was performed 6 months later, but only chronic inflammation and fibrosis was found. However, a 7-day-course of chemotherapy with cyclophosphamide, prednisolone, and vincristine was given. Two weeks later, his left elbow became painful and swollen with local heat and erythema. The neck LNs enlarged progressively with abscess formation. The LN aspirate culture had not grown any conventional bacteria after 7 days. On review in September 1994 there were 10 soft, non-tender cervical LNs sized around 0.5 to 2 cm in diameter on and the left elbow joint was erythematous and tender.

A chest radiograph was normal. Gram and acid-fast stains of the LN aspirate revealed numerous neutrophils without visible bacteria or acid-fast bacilli. A radiograph of the left elbow revealed an osteolytic lesion at the proximal left radius, compatible with osteomyelitis. An enzyme-linked immunosorbent assay (Murex Biotech Limited, Dartford, U.K.) for anti-human immunodeficiency virus (HIV) antibody was negative. The absolute CD4 count was 0.799 x 10^9/L. However, cutaneous anergy to tetanus toxoid, diphtheria toxoid, Streptococcus antigen (group C), tuberculin, Candida albicans antigen, Trichophyton antigen, and Proteus mirabilis antigen was noticed on a cell-mediated immunity assay (Multitest M.I. Institut Mérieux, Lyon, France).

After admission, the patient developed prominent local tenderness of the sternum, lumbosacral spine, and left elbow. Empirical treatment with intravenous ceftriaxone 1 g every 12 h was started. A whole-body bone scan using isotope Tc-99 m showed hot spots compatible with osteomyelitis at the sternum, left elbow, bilateral ribs, and lumbosacral spine (Fig. 1). All common bacterial cultures remained negative. However, Löwenstein–Jensen slant (Becton Dickinson, Spark, MD, U.S.A.) inoculated with LNs aspirate obtained at the time of admission grew a scotochromogen 4 weeks later. This scotochromogen was subsequently identified as M. szulgai by conventional biochemical methods. Acid-fast stain of the previously biopsied lymph node specimen revealed intracellular acid-fast bacilli in the background of chronic inflammation and fibrosis. Empirical therapy with isoniazid, rifampin, ciprofloxacin, and clarithromycin was started. The lymphadenopathy, fever, leukocytosis, and left elbow swelling gradually subsided. The isolate was reported to be susceptible to rifampin (2.5 and 5 µg/ml), ethambutol (7.5 and 15 µg/ml), streptomycin (5 and 10 µg/ml), and isoniazid (1 µg/ml), but resistant to isoniazid (0.2 µg/ml) and para-aminosalicylic acid (4 and 8 µg/ml), by the absolute concentration method. Thus, clarithromycin was changed to ethambutol. Isoniazid was discontinued in August 1995.

The patient completed 1 year of treatment with ciprofloxacin, rifampin, and ethambutol by February 1996. There were no clinical symptoms or signs indicating active disease at the end of therapy. A follow-up three-phase bone scan in February 1997 revealed no abnormal focally increased activity in flow study. One year after the completion of therapy, the patient remained well without evidence of recurrence.

Despite the lack of typical granuloma on histological examination of the LNs in our patient, M. szulgai was unlikely to be a...
<table>
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<th>Patient no.</th>
<th>Age (y), Sex</th>
<th>Manifestations and result of culture</th>
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<td>1 [2]</td>
<td>18, M</td>
<td>Multifocal osteomyelitis, mediastinal and generalized lymphadenopathy, hemoptysis, and skin lesions. Positive <em>M. szulgai</em> culture from 28 bones and two skin biopsy specimens, and sputum.</td>
<td>No underlying diseases. During treatment, prednisone had been used for a short period before the correct diagnosis was made.</td>
<td>Diminished proportion of T lymphocytes, and suppressed response to mitogens</td>
<td>Isoniazid, rifampicin, ethambutol, streptomycin, and ethionamide, and surgical drainage for 2 years</td>
<td>After 2 years of therapy, active infection still persisted.</td>
</tr>
<tr>
<td>4 [present case]</td>
<td>59, M</td>
<td>Multiple cervical lymphadenopathy, and multifocal osteomyelitis. Positive <em>M. szulgai</em> culture from lymph node aspirate.</td>
<td>No underlying diseases. Cyclophosphamide prednisolone, and vincristine (COP regimen), one course.</td>
<td>CD4 count 0.799 × 10^9/L.</td>
<td>Rifampicin, ethambutol, and ciprofloxacin for 1 year.</td>
<td>Complete remission.</td>
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[Ref]: Reference COPD: Chronic obstructive pulmonary disease
contaminant given that intracellular acid-fast bacilli were visible and the patient responded to antimycobacterial therapy.

There have been only three previously reported cases of human disseminated M. szulgai infection.2-4 All of them were associated with evidence of immunodeficiency. The clinical characteristics of the four cases (including ours) are summarized in Table I. There was no identifiable underlying disease when symptoms of M. szulgai infection first appeared in our patient. However, the chemotherapy prescribed due to initial misdiagnosis resulted in intragenic immunosuppression. This probably contributed to the dissemination of M. szulgai and the cutaneous energy demonstrated on admission. The initially depressed CD4+ count, which may also have been due to mycobacterial infection per se, returned to normal range after therapy.

The experience of treatment for disseminated M. szulgai infection is limited. Despite variation in the susceptibility patterns, most strains are susceptible to rifampicin and ethambutol.5 For pulmonary disease, a combination therapy of three in vitro active drugs is recommended, due to apparently fewer relapses compared with a two-drug regimen.6 Disseminated M. szulgai infection is more difficult to treat than pulmonary or other localized infections.7 Immunosuppression should be reversed if possible and combination therapy with three or more drugs effective in vitro is reasonable. Gur et al.8 reported a case of disseminated M. szulgai infection with multifocal osteomyelitis that responded poorly to conventional antituberculous therapy including isoniazid, rifampicin, ethambutol, streptomycin, and ethionamide. Although the organism was susceptible to these agents in vitro, active infection persisted despite 2 years of multiple drugs treatment along with repeated surgical debridement. Ciprofloxacin and clarithromycin, not commonly chosen agents, were used in our patient. M. szulgai isolates susceptible to ciprofloxacin and clarithromycin were also shown to be active against M. szulgai in vitro.9-10 Unfortunately, the in vitro susceptibility tests of these two drugs had not yet been standardized. The in vitro susceptibility tests of the M. szulgai isolate to ciprofloxacin and clarithromycin were not performed in our case. It is not known whether clarithromycin contributed to the successful outcome. Nevertheless, a combination therapy with ciprofloxacin, rifampicin, and ethambutol is proved to be successful in our patient.

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Mycobacterium tuberculosis is not an obligate aerobe

Sir,

Classical microbiological teaching describes Mycobacterium tuberculosis as an obligate aerobe1. This concept needs review after the recently published complete genome sequence of Mycobacterium tuberculosis2, which demonstrates the potential to synthesize enzyme pathways involved in anaerobic respiration.

The belief that this organism is an obligate aerobe originated from observations published earlier in this century, that Mycobacterium tuberculosis loses its viability when exposed to an environment with reduced oxygen tension3. The relevance of these experiments is questionable in the light of in vivo evidence that after termination of replication, the same number of viable, virulent bacilli persist for an extended period of time4. Furthermore, viable bacilli can be recovered from enclosed, oxygen-deprived tuberculous lesions in human surgical specimens of patients whose sputum contains no detectable tubercle bacilli5.

Although rapid death and autolysis of Mycobacterium tuberculosis occurs after abrupt depletion of oxygen, they can shift into a state of dormancy if allowed to settle slowly through an oxygen gradient6. In unagitated broth cultures, net arithmetic growth results from continued logarithmic replication of a small proportion of mycobacteria suspended in the upper, oxygen-rich layers, that is balanced by dormant forms that have settled into the oxygen-poor sediment7. The settling process forms part of adaption to survival under anaerobic conditions as the bacilli in the sediment exhibit synchronised replication when they are resuspended and diluted into an oxygen-rich medium. Tubercle bacilli that settle through an oxygen depletion gradient undergo an orderly metabolic shift-down with increased activity of enzymes involved in the glyoxylate pathway to provide a substrate for the regeneration of NAD8.

Therefore, although Mycobacterium tuberculosis thrives in an aerobic environment, it possesses the genetic and biochemical capability of anaerobic survival, and can persist experimentally in oxygen-depleted media. Tubercle formation, with its oxygen depleted environment, is a defining characteristic of tuberculosis, and surely the ability to withstand anaerobic conditions is essential to the survival of this organism.

The completion of the H37Rv genome project has far reaching implications for the understanding of the biology of this

References

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