Successful Treatment of Pulmonary Mycobacterium xenopi Infection in a Natural Killer Cell–Deficient Patient with Clarithromycin, Rifabutin, and Sparfloxacin

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Isolation of *Mycobacterium xenopi* from the respiratory tract may indicate pneumonia, often clinically indistinguishable from tuberculosis. Resistance to the classic antituberculous drugs renders the treatment of these infections problematic. We report on a case of cavernous pneumonia caused by *M. xenopi* in a 36-year-old male with natural killer cell deficiency but without severe immunodeficiency. He was successfully treated with a novel triple-drug combination comprising clarithromycin, sparfloxacin, and rifabutin. An impressive subsequent regression of pathological pulmonary changes was observed, and mycobacteria could no longer be detected. The therapeutic potential of clarithromycin and sparfloxacin in the treatment of *M. xenopi* infections is discussed.

*Mycobacterium xenopi* is a ubiquitous thermophilic bacterium occurring predominantly in water; its detection in clinical samples is usually associated with contamination or asymptomatic transient colonization [1–4]. However, in the past few years an increasing number of clinically relevant *M. xenopi* infections, including nosocomial transmissions, have been reported [5–9]. A common route of infection is aerosol spread via inhalation of contaminated water. Clinical and radiological examinations reveal pulmonary inflammation with cavitary lesions, not easily distinguishable from tuberculosis [2, 3, 7–17].

Patients with a serious history of lung disease or severe immunodeficiency due to different causes (e.g., AIDS or organ transplantation) are most commonly affected [5, 9, 18–26]. Disseminated *M. xenopi* infection is rarely observed [27, 28]. In a recently published study, clinically relevant disease was diagnosed for 10 of 103 patients from whom *M. xenopi* was isolated [5]. Therefore, it is difficult to determine the etiologic role of this bacterium and the resulting therapeutic indications.

We report herein a young man with severe pulmonary *M. xenopi* infection successfully treated with a novel combination therapy. Although severe immunodeficiency could be excluded, there was a great reduction in the number of natural killer cells (NKC).

Case Report

A 36-year-old man underwent surgery of the left lung in 1985 because of spontaneous pneumothorax. In 1987 he developed Crohn’s disease, and in 1990 he underwent a subtotal colectomy. He was treated continuously with mesalazine and temporarily with corticosteroids. Bilateral apical pleural fibrosis (right > left) and cavernous changes in the left apical region were first detected on a chest radiograph in December 1993. Despite a history of smoking 30 cigarettes per day since 1977, there was no evidence of chronic obstructive lung disease or prior pulmonary tuberculosis. Because of increased activity of the Crohn’s disease, 30 mg of methylprednisolone per day was administered between July and October 1995. In September recurrent coughing and night sweats occurred, leading to admittance to the hospital in December due to progressive deterioration (e.g., subfebrile temperature and loss of weight [5 kg over 4 months]).

Radiological examinations revealed extensive infiltrative and fibrous opacification and additional cavernous changes in the upper lobe of the left lung (figure 1, left). Since the tuberculin skin reaction was positive and acid-fast rod-shaped bacteria were detected upon microscopic examination in five sputum specimens obtained on subsequent days, antituberculous therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide was initiated. The cultivated slowly growing, scotochromogenic mycobacterium could be unequivocally identified as *M. xenopi* by determination of the signature sequence of both the 16S-rDNA and the *dnaJ* gene [29, 30].

With use of the radiometric BACTEC method (Becton Dickinson, Heidelberg, Germany) at 42°C (the optimal growth temperature for *M. xenopi*), drug-susceptibility testing showed susceptibility to rifampicin and streptomycin but revealed resistance to isoniazid, ethambutol, and pyrazinamide. Etests (AB Biodisk, Solna, Sweden) performed on Middlebrook 7H10
agar at 42°C revealed a very low MIC for clarithromycin (0.016 mg/L) and sparfloxacin (0.003 mg/L) but a high MIC of 6.0 mg/L for ciprofloxacin.

HIV serology was negative. Mild leukocytosis (11,600 lymphocytes/μL), with 1,276 lymphocytes/μL detected before initiation of therapy, was due mainly to (1) a reduction of CD8/CD11b coexpressing suppressor T lymphocytes (STLs) and (2) a reduction of CD16/CD56 coexpressing NKCs. The number of CD4+ T cells was normal. Because of the deficiency of STLs, the CD4/CD8 ratio and the ratio of CD8+/CD11b− cytotoxic T lymphocytes (CTLs) to STLs were elevated (table 1). At this time, the 3H-thymidine incorporation rate by the patient’s cultured lymphocytes was five times higher than that of healthy controls.

The mitogens phytohemagglutinin and concanavalin A and the recall antigen zymosan increased the 3H-thymidine incorporation rate of these basally stimulated lymphocytes by a much lower factor in the patient than in healthy controls. Conversely, the 3H-thymidine incorporation by the patient’s lymphocytes increased dose-dependently after stimulation with tuberculin by up to 8 times the basal incorporation rate.

After species identification and drug-susceptibility testing, the treatment was switched to an alternative triple-drug regimen in January 1996, involving daily doses of 500 mg of clarithromycin, 200 mg of sparfloxacin, and 300 mg of rifabutin. Smears became negative within 6 weeks, and a negative sputum culture was achieved within 3 months. The overall 12-month antibiotic treatment led to an impressive regression of the laboratory and radiological changes (table 1 and figure 1, right). All 3H-thymidine incorporation rates normalized, but numbers of NKCs and STLs remained as low as in the baseline tests (table 1).

The drug regimen was tolerated well. Photosensitization, a well-known side effect of sparfloxacin, was managed by...
light protection. Activity of Crohn’s disease was controlled by mesalazine monotherapy. Because of the favorable clinical course, therapy was stopped after 12 months. No evidence of recurrence was found in the subsequent follow-up period (2 years).

Discussion

*M. xenopi* was clearly proven to be the etiologic agent of the cavitary pulmonary changes found in the present case. The possibility of misidentification of *M. xenopi as Mycobacterium celatum* was unequivocally excluded [29–31]. Because of the repeated isolation of *M. xenopi* and the exclusion of a simultaneous *Mycobacterium tuberculosis* infection, the diagnostic criteria for a nontubercuload infection were fulfilled [1]. The high reactivity of the patient’s lymphocytes to tuberculin could be explained by the well-known cross-reactivity in cases of *M. xenopi* infections [32]. However, an earlier infection with *M. tuberculosis* could not be definitively excluded.

The long-term corticosteroid therapy certainly represents a risk for secondary infections [33], but the subset of CD4 T cells responsible for regulating the immune response to *M. tuberculosis* [34–36] was not impaired; our patient had normal CD4 cell counts and a strong reaction to PPD. The CD8 T cell subpopulation involved in immune response to *M. tuberculosis* is the CD11b– CTLs [36–41]. It is notable that in our patient the reduction of CD8 T cells was not due to the CTLs but to the T suppressor cells.

NKCs are also known to contribute to the immune response to mycobacteria, mainly mediated by a T cell–independent IFN-γ secretion [42]. In patients with active ileocecal Crohn’s disease, oral corticosteroids are known to cause a temporary suppression of activity in peripheral blood NKCs [43] by repression of the synthesis of perforin mRNA and granzyme A and reduced adhesion to target cells [44]. Therefore, in our patient temporary suppression of the NKC function by corticosteroids might have contributed to development of the *M. xenopi* infection.

Despite the lack of clinical signs of obstructive lung disease, the presence of further pulmonary damage has to be assumed in view of the patient’s long-term nicotine abuse. Malnutrition (body mass index, 18.3 kg/m²) associated with Crohn’s disease might have been a further risk factor. Our case demonstrates that young adults without evidence of severe immunodeficiency may develop a clinically relevant pulmonary *M. xenopi* infection if other predisposing factors exist.

Chemotherapeutic combination protocols with three to four drugs and an overall treatment duration of 18–24 months usually are recommended in cases of *M. xenopi* infection [1, 5, 12–16]. On the basis of results of vitro susceptibility testing, we selected a combination of clarithromycin, rifabutin, and sparfloxacin for therapy. However, clinical response to chemo-therapy is variable and difficult to predict, and no proven correlation with in vitro test results could be found [1, 10, 11]. Surgery therefore represents an important alternative to drug therapy for patients with localized pulmonary disease [10, 11, 32, 45].

The prophylactic and therapeutic efficacy of rifabutin and newer macrolides such as clarithromycin and azithromycin against nontubercuload mycobacteria has been convincingly demonstrated [46–55]. Therefore, they are used in many combination regimens for nontubercuload mycobacterial infections, including those due to *M. xenopi* [50–52]. In vitro findings have shown excellent activity of sparfloxacin against nontubercuload mycobacteria, including strains of *M. xenopi* [56, 57]. High tissue concentrations of sparfloxacin are achieved by oral administration [58].

Pronounced synergy between sparfloxacin and clarithromycin as well as rifabutin has been observed in vitro [55, 59]. MICs of sparfloxacin were much lower than those of ofloxacin, levofloxacin, and, as also seen in our case, ciprofloxacin [59–61], a finding indicating that sparfloxacin may be the most potent quinolone against susceptible mycobacteria [62].

The triple-drug combination of clarithromycin, rifabutin, and sparfloxacin used in the present case has not been reported so far for nontubercuload mycobacterial infections. However, successful treatment of an extrapulmonary infection with clarithromycin and sparfloxacin has recently been described [63]. Despite its photosensitization side effect, sparfloxacin may be a valuable drug for treatment of *M. xenopi* infections.

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References


