# ABOUT TWO CASES OF *MYCOBACTERIUM SIMIAE* INFECTION IN AIDS: REVIEW OF THE PATHOGENICITY

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## ABSTRACT

*Mycobacterium simiae* is an ubiquitous species rarely involved as a cause of human infection. Its pathogenicity remains therefore unclear and controversial. Disseminated infections with *M. simiae* occur rarely and only 7 cases have been reported in patients with acquired immunodeficiency syndrome (AIDS). At least, two were mixed infections caused by *M. simiae* and *M. avium-intracellulare.*

We report the case of two AIDS patients presenting with pure *M. simiae* infections : one was a disseminated infection and the other a pulmonary infection. Epidemiology and pathogenicity of *M. simiae* in pulmonary, extra-pulmonary and disseminated infections are reviewed.

## INTRODUCTION

*Mycobacterium tuberculosis* has been historically and epidemiologically recognized as a major pathogen, but the awareness and frequency of infection caused by the so-called non-tuberculous mycobacteria (NTM) have only recently increased in patients with the acquired immunodeficiency syndrome (AIDS)(1-6). In developed countries, NTM disease is detected antemortem in 18 to 27 percent of patients with AIDS and found in half of autopsied patients (5-8). Most of these NTM infections are caused by *Mycobacterium avium - Mycobacterium intracellulare* (MAI). However, *M. kansasii, M. marinum, M. scrofulaceum, M. szulgai, M. xenopi, M. fortuitum, M. asiaticum, M. haemophilum , M. malmoense, M. gordonae, M. flavescens* and *M. smegmatis* have also been reported in AIDS patients, some being described in association with *MAI* (9,10). *M. simiae* has been identified in seven AIDS patients. At least two of them were co-infected with *MAI* while two presented with pure *M. simiae* infection (6,11,12). We report two AIDS patients with *M. simiae* infection (disseminated, and pulmonary form) and review the epidemiological and pathological aspects of *M. simiae* human infections.

## CASE REPORTS

### Case report 1

A 44-year-old African heterosexual patient was found HIV-positive in September 1987, when he presented with oral hairy leucoplakia and ophtalmic zoster. The patient was a business man living in Burundi but travelling regularly to Belgium for medical care. At that time, his body weight was 95 kg. His CD4 cell count was 67/mm$^3$.

In November 1989, a chest roentgenogram showed a left infiltrate with cavitation. *M. tuberculosis* was isolated and the patient was treated with isoniazid, rifampicin and ethambutol.

In September 1990, *Pneumocystis carinii* pneumonia was suspected in Burundi and cotrimoxazole was started. Despite therapy, the patient remained unwell, with ongoing low grade fever, productive cough and progressive weight loss.

In November 1990, cultures of sputum and bronchovalveolar lavage fluid (BAL) did not yield significant pathogens. Stainings of BAL and sputum for acid-fast bacilli were negative. The patient was treated with physical therapy, ofloxacin and subsequently roxithromycin with slight improvement. In March 1991, a sputum induction revealed acid-fast bacilli further identified as *M. simiae.*

In July 1991, the patient still presented with fever, dyspnea, productive cough and a 21kg body weight loss. Physical examination revealed hepatomegaly and several subcutaneous nodules, either crusted or ulcerated. Chest X ray was normal. His CD4 cell count was 11/mm$^3$. Skin biopsies showed a lymphocyte and monocyte-macrophage infiltrate in the absence of granulomatous reaction. Cultures from blood,

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sputum, BAL and skin biopsy yielded *M. simiae*. Stainings of blood, sputum, BAL and skin sections did not reveal acid-fast bacilli. Treatment with rifabutin (450 mg/d) and clofazimine (100 mg/d) was instituted. Shortly after, the patient developed AIDS-related encephalopathy and returned to Burundi. He remained febrile and cachectic and had persisting cutaneous lesions which did not improve. While no complementary informations were provided about the patients compliance to antimycobacterial therapy, he died in January 1992.

**Case report 2**

A 44-year-old Belgian patient with a past medical history of Herpes zoster infection, was found HIV-positive in 1990 when he presented with *Candida* oesophagitis. The patient was heterosexual and had lived ten years in Africa. His body weight was 64kg. His CD4 cell count was 50 per $mm^3$.

In November 1991, he presented with a *Mycobacterium kansasii* pulmonary infection and was treated with rifampicin, pyrazinamide, isoniazid and streptomycin with slight improvement. At that time, his CD4 cell count was $1/mm^3$.

In June 1992, the patient consulted because of a productive cough, asthenia and headache. A chest X-ray was normal. Stainings of sputum for acid-fast bacilli were positive and cultures yielded *M. simiae*. Culture of cerebrospinal fluid was positive for *Cryptococcus neoformans* and the patient was treated with fluconazole, clarithromycin, rifampicin, ethambutol and trimethoprim/sulfamethoxazole.

In January 1993, the patient presented with severe headache, thoracic pain and a productive cough. The chest X-ray was still normal. Cerebrospinal fluid was positive for *C. neoformans* and sputum cultures yielded *Pseudomonas aeruginosa* and *M. simiae*. His body weight was 52kg, his CD4 cell/count was $1/mm^3$.Treatment with ciprofloxacin and amphotericin B was ineffective. In March 1993, the patient decided to withold therapy and died at home.

## MICROBIOLOGICAL DATA

The isolates were identified by conventional methods (13-15) and antimicrobial sensitivity tests were performed on Löwenstein-Jensen slants by the method of Canetti et al (15). The mycolic acids, the main components of the mycobacterial cell walls, were analyzed by one-dimensional thin-layer chromatography (16-18). The fatty acids were studied by gas chromatography (GC) (19). Peak identification was performed by GC-mass spectrometry analysis in the electron impact mode (20). All the mycobacterial strains were identified as *M. simiae* by their cultural, physiological and biochemical properties: smooth photochromogenic colony form, no growth at 45°C, positive for urease and 68°C catalase and negative for Tween 80 hydrolysis, arylsulfatase, nitrate reductase and niacin production. The mycolate profile of all isolates showed the characteristic patterns of *M. simiae*: $\alpha$, $\alpha'$ and keto mycolates.

GC and GC-mass spectrometry analysis also gave results compatible with *M. simiae* and identical for all strains : hexacosanoate was the predominant mycolate cleavage product and no branched-chain fatty acids apart from tuberculostearate were detected.

The isolates were susceptible to 8 mg/ml ciprofloxacin and resistant to 40 mg/ml rifampicin, 40 mg/ml rifabutin, 2 mg/ml ethambutol, 0,2 mg/ml isoniazid, 4 mg/ml streptomycin, 20 mg/ml ethionamide, 2 mg/ml thiacetazone and 4 mg/ml clofazimine.

## EPIDEMIOLOGY

Originally isolated in 1965 from a colony of *Macacus rhesus* monkeys imported from India to Hungary (21), *M. simiae* has subsequently been found in Europe(22,23), in Africa (24), in Asia (25), and the United States (26-28). In Cuba, Valdivia isolated 45 strains of *M. habana* (later identified as *M. simiae*), mostly from patients with chronic pulmonary tuberculosis (29). In Israël, from 1975 to 1981, 399 strains of *M. simiae* were isolated (30). Noteworthy, *M. simiae* had also been isolated from tap water in Gaza (28) and from soil samples collected in Central Africa (31,32), in USA (Louisiana and Florida) and in Australia (33,34 and F. Portaels, unpublished data). In a study of mycobacterial flora in the stools of 50 healthy Europeans, mycobacteria were isolated from more than 50% of the stools, with a predominance of *M. simiae* (28% of the stool specimens) (35). In another study in Japan, Mori detected *M. simiae* in 18% of 49 skin samples and in 8% of umbilical cords of babies born by caesarian section (36). Since this organism is commonly found in nature, contamination of cultured material or transient colonization does occur and a single positive culture does not prove its pathogenicity.

## PATHOGENICITY

**Pulmonary infections**

The role of *M. simiae* as pulmonary pathogen is supported by detailed case reports from immunosuppressed patients or patients with preexisting pulmonary lesions, such as tuberculosis, carcinoma, fibro-

sis, bronchiectasis or chronic obstructive lung disease (6,23,3742).

In Texas, from 1974 through 1981, *M. simiae* was isolated from the sputum of 24 patients. Two met definitive criteria for infection whereas three probably had progressive granulomatous disease caused by *M. simiae* . In 19 patients, there was no evidence of pathologic processes caused by *M. simiae* (39). From 1981 through 1983, 67 isolates of *M. simiae* were reported by the Centers for Diseases Control in the United States, but they were considered as potential pathogens in 14 instances (26). During a period of 11 years (1983-1993), 137 clinical isolates of *M. simiae* were obtained from 75 patients in San Antonio (Texas). Most of these isolates (93%) were recovered from a pulmonary source. *M. simiae* isolation from sputum was indicative of definite infection in only 3 of 62 evaluable patients. Nine (14%) had probable disease and 48 (76%) were thought to be colonized (6).

In Cuba, Valdivia et al isolated 45 strains of *M. simiae*, mostly from patients with chronic pulmonary tuberculosis (n=35). In 44 of these cases, *M. tuberculosis* was also isolated. In 8 cases, the isolation of *M. simiae* was considered as clinically significant.

In Israel, from 1975 to 1981, 399 strains (35) of *M. simiae* were isolated from 287 persons, all but one living in the coastal plain of Tel-Aviv (30). Of the 18 patients with multiple isolations, most had an history of pulmonary tuberculosis. According to the authors, these cases did not provide substantial evidence of the pathogenicity of *M. simiae*. The great majority of isolates were indeed considered to be from environmental sources. Accordingly, Lavy et al. concluded that *M. simiae* was capable of prolonged or temporary colonization of previously damaged lungs.

Noteworthy, identification methods are not always described and *M. simiae* is sometimes found in association with other NTM. Moreover, these cases do not always meet the criteria of pathogenicity as recommended by the American Thoracic Society (42). In the absence of histopathological specimens, the case report 2, is considered as a probable infection. Indeed, *M. simiae* was isolated in three sputum specimens, in the presence of persistent pulmonary symptoms.

In summary, *M. simiae* isolation from sputum is rarely indicative of infection; nevertheless, careful follow-up is necessary especially in immunosuppressed individuals or in patients with underlying bronchopulmonary disease. In contrast to patients with *M. simiae* disease, colonized patients usually have negative initial smears, fewer positive cultures and lighter yields of organisms on the few positive cultures.

**Extrapulmonary infections**

Extrapulmonary *M. simiae* infections have been described in patients without apparent immunosuppression (6,43-45). However, the cases with sternal osteomyelitis (43) and with chronic pyclonephritis (44) were mixed infections caused by *M. simiae* and *M. fortuitum* and *M. kansasii*. respectively. In another case of suspected osteomyelitis, *M. simiae* was isolated from a degenerating disk in a female patient showing no disease progression despite the lack of antimycobacterial treatment (43). Interestingly, *M. simiae* was also isolated from ascitic fluid in a Nepalese woman who developed an intra-abdominal infection one week after forceps-assisted vaginal delivery. She was successfully treated with combination chemotherapy (rifampicin, isoniazid, pyrazinamide, ofloxacin and kanamycin) (45). A case of cutaneous infection was also reported in Texas, in a woman successfully treated by clofazimine, dapsone and thalidomide(6). Thusfar, the role of *M. simiae* as an extrapulmonary pathogen has only been well established in these latter two cases.

**Infections in AIDS patients**

Disseminated infections have been reported in seven patients with AIDS (6,11,12). A mixed infection with M. avium (MAI) and *M. simiae* was reported in France in an African man who presented with malnutrition and a Whipple-like disease of the gastrointestinal tract. Cultures of blood, jejunal fluid and rectal biopsy yielded *M. simiae*. Another patient coinfected by *M. simiae* and MAI was reported in the USA, in a Puerto Rican patient with a febrile wasting illness. Recently, fatal *M. simiae* infection was reported in two Israeli patients with AIDS. In both patients, *M. simiae* was isolated from blood. It was also found in cultures of sputum and bone marrow from the patient with cavitary pulmonary infiltrates. Three other cases were described in Texas (6), *M. simiae* being isolated from blood, bone marrow, brain and sputum. A description of the nine previously reported patients is presented in Table 1.

## DISCUSSION

In our first patient, *M. simiae* was recovered from multiple sites including blood, sputum, broncho-alveolar fluid and skin biopsy (46). Furthermore, *M. simiae* was the only microorganism isolated, clearly demonstrating the pathogenic role of *M. simiae*. In our second report, *M. simiae* was isolated three times despite antimycobacterial therapy. At that time, *M.*

**TABLE 1. CLINICAL FEATURES OF PATIENTS (N=9) WITH M.SIMIAE AND HIV INFECTION**

| Patients | Age (y)/ Sex | Origin | Clinical Presentation | CD4 cell count | Outcome | Sites of isolation of M.simiae | Other mycobacteria isolated | Therapy |
|---|---|---|---|---|---|---|---|---|
| 1 | 43/M | Congo referred to France | Malnutrition Whipple-like disease | 100/mm$^3$ | lost to follow-up | blood, jejunal fluid, rectal biopsy | MAI | No |
| 2 | 30/M | Puerto Rico leaving in N.Y city | fever, wasting, intraabdominal adenopathy, cholostasis | NA | death (3 months) | blood | MAI | -RNIP.PZA.INH -CLOFA, EMB added later -ETHIO, CYCLO added later |
| 3 | 18/M | Israel | fever, cough, pulmonary infiltrate and cavitary lesion | 100/mm$^3$ | death (3 months) | sputum, blood, bone marrow | No | CIPRO |
| 4 | 21/M | Israel | fever, wasting | NA | death (5 days) | blood | No | No |
| 5 | 25/M | Texas? | fever wasting | 48/mm$^3$ | death (10 days) | blood | NA | No |
| 6 | 33/M | Texas? | cough, dyspnea | 15/mm$^3$ | death (6 months) | bone marrow sputum | NA | -INH.RNIP.1EMB -CLARI.CIPRO, added later |
| 7 | 38/M | Texas? | fever, wasting | 23/mm$^3$ | death (10 weeks) | sputum, blood, brain | NA | No |
| 8 | 44/M | Burundi referred to Belgium | fever, productive cough, wasting, subcutaneous nodules | 11/mm$^3$ | death (6 months) | skin, blood, sputum, BAL | No | -RBT.CLOFA |
| 9 | 44/M | Belgium having lived in Central Africa | cough, wasting | 1/mm$^3$, | death (9 months) | sputum | No | -RMP.EMB CLARI.CTX -CIPRO added later |

Definition of abbreviations: NA: non available; RMP: rifampin; PZA: pyrazinamide; INH: isoniazid; CLOFA: clofazimine; EMB: ethambutol; ETHIO: ethionamide; CICLO: cicloserine; CIPRO: ciprofloxacin; RBT: rifabutin; CTX : cotrimoxazole;

*kansasii* was no more isolated and the patient still presented pulmonary symptoms.

The first patient presented with skin lesions. Cutaneous infection is a relatively uncommon form of mycobacteriosis (47-50) and it has been previously reported only once in *M. simiae* infections (6). The absence of a classic granulomatous inflammation on skin biopsy may seem intriguing. However, this histologic picture is often observed in AIDS patients infected by MAI and reflects the inability of the host to raise an effective immune response (4,50-53). Since disseminated disease may present as cutaneous lesions, skin lesions of unknown origin should be promptly biopsied in immunocompromised patients. Because histologic findings may not be specific, it is important that smears and cultures for mycobacteria be systematically performed.

*M. simiae* is a photochromogenic (pigment production in light) acid-fast bacillus. In some clinical isolates pigment production can be slow or scant and the organism may resemble MAI. Use of the niacin test may differentiate the species. *M. simiae* may also easily be confused with *M. scrofulaceum*. Indeed, the two traditional tests, pigment production in light (photochromogenicity) and niacin acculumation are not always sufficiently pronounced to differentiate between the two species. Although *M. scrofulaceum* produces consistently negative results in both tests, *M. simiae* has positivity rates of 83% for photochromogenicity and 37% for niacin accumulation (54). Therefore, analysis of fatty and mycolic acid patterns may be necessary to confirm the identity of *M. simiae*. *M. simiae* patterns are similar to those of *M. genavense*. Although *M. simiae* grows on Löwenstein-Jensen medium and is usually photochromogenic which is not the case for *M. genavense*, distinction between these two mycobacteria may sometimes require analysis of their 16 S rRNA. Although correct identification of mycobacterial isolates may not appear clinically mandatory, the encouraging results of recent therapeutic trials (6,57-60) and the existence of mixed mycobacterial infections make identification of all mycobacterial isolates imperative for the guidance of appropriate therapy.

Therapy of M. *simiae* infection remains a difficult problem. *In vitro* succeptibility testing demonstrates resistance to the conventional antituberculous drugs, although Valero et al (6) observed 31% susceptibility to streptomycin. Agents with some in vitro activity include ethionamide, cycloserine, clofazimine, amikacin and ciprofloxaxin. In a murine model of disseminated infection, rifampin, clofazimine and

amikacin demonstrated activity against two *M.simiae* strains (60). In another study (59), claritromycin, ofloxacin and claritromycin plus ethambutol demonstrated a significant decrease in the level of infection in both lung and spleen tissues. According to the American Thoracic Society (42), initial therapy may be started with a four-drug regimen (clarithomycin, ethambutol, rifabutin and streptomycin). Further modifications should be made according to susceptibility tests.

To conclude, *M. simiae* is an unfrequent cause of pulmonary, extrapulmonary and disseminated infection. However, accumulating data highlights its pathogenic potential. A careful follow-up is therefore mandatory when *M. simiae* is isolated. This is especially true in immunosuppressed patients or in patients with underlying bronchopulmonary disease.

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