Disseminated Infection with a Mycobacterium Related to *Mycobacterium triplex* with Central Nervous System Involvement Associated with AIDS

Valérie Zeller,1 Anne-Lyse Nardi,1 Chantal Truffot-Pernot,2 Wladimir Sougakoff,2 Bruno Stankoff,3 Christine Katlama,1 andFrançois Bricaire1

Service des Maladies Infectieuses et Tropicales,1 Laboratoire de Bactériologie et Centre National de Référence de la Résistance aux Antituberculeux,2 and Fédération de Neurologie,3 Pitié-Salpêtrière Hospital, Paris, France

Received 28 May 2002/Returned for modification 9 July 2002/Accepted 29 January 2003

We report on a case of disseminated infection with central nervous system involvement due to an atypical mycobacterium related to *Mycobacterium triplex* in a severely immunodepressed human immunodeficiency virus-infected man.

CASE REPORT

A 41-year-old Nigerien man was admitted to hospital on 10 April 2001 with fever, cachexia, edema, and diarrhea. Human immunodeficiency virus type 1 (HIV-1) infection had been diagnosed 6 months previously in Niamey, Niger, and the patient had received combination antiretroviral therapy with stavudine and didanosine.

On admission, his temperature was 38.2°C. The patient was cachectic and had severe bilateral edema of the lower limbs and a markedly swollen abdomen with fluid accumulation. He complained of a nonproductive cough. Cardiac, chest, and neurologic examinations were normal. No lymphadenopathy or hepatosplenomegaly was found. HIV-1 infection was confirmed by Western blotting. The CD4-cell count was 17 mm3, and the plasma HIV load was 82,000 copies ml-1. The findings on chest radiography and bronchoscopy were normal. Sputum smears revealed acid-fast bacilli. Genotypic amplification of the *Mycobacterium tuberculosis* complex (Amplified *M. tuberculosis* direct test; Gen-Probe) was negative, and the bacilli were identified as atypical mycobacteria. One month later a slowly growing mycobacterium was isolated from sputum, ascitic fluid, and blood. Hybridization with the Accuprobe for the *Mycobacterium avium* complex (Gen-Probe) was negative, although the results of cultural and biochemical tests were close to those for *M. avium* complex strains (slow growth rate; small, smooth, and slightly pigmented colonies; no biochemical activity except catalase and urease activities). The isolate was finally identified as being related to *Mycobacterium triplex* by partial 16S rRNA sequencing (the strain is available at the EMBL database). We found 98% sequence identity (four mutations over a 299-nucleotide fragment) with an *M. triplex* variant (isolate 23; EMBL accession number AJ276890) (7). The antibiotic susceptibility of the strain was close to that of *M. avium*; the strain was susceptible to clarithromycin, moderately susceptible to rifabutin and ethambutol, and probably resistant to amikacin (MICs on Loewenstein-Jensen medium were 2, 4, and 32 mg/liter, respectively); when the susceptibility of the isolate was tested by the proportion method on Loewenstein-Jensen medium, it appeared to be resistant to all antituberculous drugs except cycloserine and ethionamide.

Antimycobacterial treatment with isoniazid, rifampin, ethambutol, clarithromycin, and pyrazinamide was started on 13 April, followed 2 weeks later by antiretroviral therapy with a combination of zidovudine, lamivudine, ritonavir, and indinavir. The patient’s condition improved initially, but 2 weeks after the start of antiretroviral therapy, he again developed fever, diarrhea, and ascites, as well as involuntary arhythmic movements of a forcible, rapid, jerky type and of a wide range and a flinging nature. The movements involved the proximal and distal parts of the upper and lower limbs, predominating in the arm, and were restricted to the left hemibody. They were uncontrollable and were greatly increased by the patient’s attempts to move his left side. This movement disorder was typical of left hemiballism-hemichorea. Magnetic resonance imaging (MRI; T2-weighted sequences and fluid-attenuated inversion recovery acquisition) showed a lesion in the subthalamic region that extended to the lower part of the thalamus (Fig. 1B and C); T1-weighted sequences showed mild gadolinium enhancement (Fig. 1A). Cerebrospinal fluid examination showed mild inflammation, with 6 leukocytes ml-1, 0.53 g of protein liter-1, and a low glucose concentration (1.5 mmol liter-1). PCRs for herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, JC virus, and human herpes virus 6 in cerebrospinal fluid were negative, as were serological tests for syphilis and cryptococcal antigen and cryptococcal staining (Giemsa staining). Culture of the cerebrospinal fluid yielded the same slowly growing acid-fast bacillus. The patient’s plasma was positive for immunoglobulin G antibodies against *Toxoplasma gondii.*
A paradoxical worsening of the mycobacteriosis was suspected, and antiretroviral therapy was stopped on 12 May. Treatment with clarithromycin, ethambutol, and rifabutin was maintained and the patient became afebrile; the diarrhea gradually disappeared and the ascites resolved. The movement disorders improved within a few weeks, and the lesion detected by cerebral MRI regressed by week 16 (Fig. 2). Cerebrospinal fluid examination showed a lower protein concentration (0.33 g liter\(^{-1}\)), a higher glucose concentration (2.6 mmol liter\(^{-1}\)), and no cells; however, culture on Loewenstein-Jensen medium still yielded the same mycobacteria. The pattern of susceptibility to antituberculous drugs was unchanged.

Antiretroviral therapy with didanosine, zidovudine, indinavir, and ritonavir was reintroduced on week 7 of antimycobacterial therapy. After 2 months of this treatment, the viral load fell from 82,000 to below 200 copies ml\(^{-1}\); the CD4-cell count remained low (17 ml\(^{-1}\)).

Despite these treatments as well as treatment with an antidepressant and psychological assistance, the patient remained cachectic, had severe depression, and refused food. He was discharged to home and died 5 months after the start of antimycobacterial treatment.

**Discussion.** *M. triplex* was first characterized in 1996 by Floyd et al. (3). This new, slowly growing, nonpigmented mycobacterial species was identified by analysis of the 16S RNA hypervariable region. Phylogenetic analysis of the 16S rRNA showed that *M. triplex* was closely related to *Mycobacterium simiae* and *Mycobacterium genavense* (3).

The case of severe disseminated infection with central nervous system involvement due to a mycobacterium related to *M. triplex* described here occurred in a profoundly immunodepressed patient. Hemichorea-hemiballism was associated with a lesion in the subthalamic region. In patients with AIDS, hemichorea-hemiballism is most frequently associated with *Toxoplasma* abscesses (6). Here, infection of the central nervous system by an organism related to *M. triplex* was strongly suggested by (i) positive cerebrospinal fluid culture; (ii) good neurological and radiological responses to antimycobacterial treatment; and (iii) no signs of active toxoplasmosis, despite the absence of a specific treatment.

Five cases of human infection with *M. triplex* or related organisms have been reported (1, 2, 4, 5, 7) (Table 1): three adults with severe HIV-related immunodeficiency, one adult with drug-induced immunodeficiency, and a 4-year-old immunocompetent girl. These patients had pulmonary, abdominal, pericardiac, bone and joint, or lymph node involvement. Ours is the first report of infection due to an atypical mycobacteria related to *M. triplex* with central nervous system involvement.

In our patient, treatment with antimycobacterial and antiretroviral drugs was initially successful, but the patient’s condition declined gradually because of severe depression and cachexia; culture of cerebrospinal fluid on Loewenstein-Jensen medium remained positive for an organism related to *M. triplex*.

Among the previously published cases (Table 1), three patients received antimycobacterial combination therapy, one pa-
tient received antimycobacterial drugs and surgical drainage of a bone abscess, and one patient had surgical drainage only. Four patients were considered cured 0 to 36 months after discontinuation of antimycobacterial treatment. One HIV-infected patient had a relapse after 8 months of treatment.

In conclusion, mycobacteria related to *M. triplex* cause disease similar to that caused by *M. avium* complex infection and can infect the central nervous system. This species must be borne in mind if the results of tests with standard genetic probes for *M. avium* complex are negative. The antimicrobial susceptibility pattern of mycobacteria related to *M. triplex* seems to be close to that of *M. avium* complex.

**Nucleotide sequence accession number.** The 16S rRNA sequence of the *M. triplex* strain has been deposited in the EMBL database under accession number AJ535505.

**REFERENCES**


**TABLE 1. Published cases of human infection with *M. triplex*-related organisms***

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Information</th>
<th>Clinical Manifestations</th>
<th>Diagnostic Methods</th>
<th>Treatment; outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cingolani et al.</td>
<td>40-yr-old HIV-positive man; HAART (CD4 count, 98 ml⁻¹; viral load, 15,000 copies ml⁻¹)</td>
<td>Fever, asthenia, and sweats; arthritis of the knee; spleen abscess; abdominal adenopathies</td>
<td>Culture of joint fluid, bone and blood</td>
<td>ETIO, CLA, surgical drainage; relapse at mo 8 of treatment (CD4 count, 34 ml⁻¹; viral load, 6,500 copies ml⁻¹)</td>
</tr>
<tr>
<td>Bajolet et al. (1)</td>
<td>47-yr-old HIV-positive man (CD4 count, 24 ml⁻¹)</td>
<td>Axillary adenopathy</td>
<td>Culture of lymph node biopsy specimen</td>
<td>INH, RFP, and ETB (3 mo) and INH and RFP (2 mo); death due to other causes after 4 mo.</td>
</tr>
<tr>
<td>Hazra et al. (4)</td>
<td>4-yr-old girl</td>
<td>Preauricular mass, submandibular adenopathy</td>
<td>Culture of lymph node biopsy specimen</td>
<td>CLA, RFB, and ETB (12 mo); cured</td>
</tr>
<tr>
<td>Hoff et al. (5)</td>
<td>13-yr-old girl; liver graft recipient; drug-induced immunodepression</td>
<td>Ascites, pericarditis</td>
<td>Culture of pericardiac fluid</td>
<td>Pericardiac drainage</td>
</tr>
<tr>
<td>Suomalainen et al.</td>
<td>67-yr-old HIV-positive man</td>
<td>Hemoptysis CT; bronchiectasis, alveolar opacities, and micronodules</td>
<td>Culture of sputum</td>
<td>CIP, RFP, and CLA (18 mo); favorable clinical and radiological outcomes.</td>
</tr>
</tbody>
</table>

* Abbreviations: HAART, highly active antiretroviral therapy; ETIO, ethionamide; CLA, clarithromycin; INH, isoniazid; RFP, rifampin; ETB, ethambutol, CIP, ciprofloxacin; RFB, rifabutin. CT, computed tomography.