Evolution of Central Nervous System Multidrug-Resistant *Mycobacterium tuberculosis* and Late Relapse of Cryptic Prosthetic Hip Joint Tuberculosis: Complications during Treatment of Disseminated Isoniazid-Resistant Tuberculosis in an Immunocompromised Host[∇]

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We report a case of disseminated isoniazid-resistant tuberculosis in an immunocompromised patient with evolution of rifampin (rifampicin) resistance in the central nervous system. This was cured with intraventricular and oral treatment but was followed by a late relapse of the original infection in a prosthetic hip joint. We provide drug levels in cerebrospinal fluid and serum.

CASE REPORT

A 39-year-old human immunodeficiency virus-seronegative man from the Philippines presented to Auckland City Hospital on 12 August 2001 with a 3-week history of midthoracic back pain and intermittent fevers and a 1-day history of lower-limb weakness and sensory loss. He had a 3-year history of systemic lupus erythematosus with renal and joint involvement and had taken prednisone (10 to 60 mg daily) and azathioprine (150 mg daily) since the diagnosis. He had had a left total hip joint replacement a year before for aseptic necrosis of his femoral head. Spinal magnetic resonance imaging (MRI) demonstrated discitis at T8/9 with a large epidural abscess and cord compression. A computed-tomography guided biopsy of spinal tissue on 14 August 2001 showed acid-fast bacilli (AFB) upon Ziehl-Neelsen staining, and subsequently *Mycobacterium tuberculosis* was isolated from this specimen and from his urine. While in hospital, he underwent flexor tendon synovectomy and median nerve decompression for left carpal tunnel syndrome. Histological examination of the excised tissue showed granulomatous inflammation and acid-fast bacilli, but the tissue was not cultured. Testing of susceptibility to first-line agents of the spinal and urinary isolates using the Bactec MGIT 960 method showed resistance to isoniazid but susceptibility to ethambutol, pyrazinamide, rifampin (rifampicin), and streptomycin (Table 1). The isolate was also susceptible to all second-line agents tested (amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide, rifabutin, and streptomycin).

On 15 August 2001, he began treatment for tuberculosis with

ethambutol, isoniazid, pyrazinamide, and rifampin (Table 1), with resolution of symptoms except for some residual leg weakness. On 18 October 2001, while on ethambutol and rifampin, he developed diplopia due to a right partial oculomotor nerve palsy. MRI demonstrated a right temporal space-occupying lesion, consistent with a longstanding meningioma not responsible for the cranial nerve palsy, and no other abnormality. Cerebrospinal fluid (CSF) was abnormal, with lymphocytosis and elevated protein (Table 1) but normal glucose, no organisms were seen on Gram or Ziehl-Neelsen stains, and culture was sterile. *M. tuberculosis* PCR and cryptococcal antigen latex agglutination tests were negative. Although central nervous system (CNS) tuberculosis was not proven, the nerve lesion and the unexplained CSF lymphocytosis strongly suggested this diagnosis, and pyrazinamide, which had been stopped 2 weeks earlier, was reintroduced. His diplopia resolved, and he made good progress.

Five months from presentation, on 25 January 2002, because of hyperuricemia and severe tophaceous gout, pyrazinamide was stopped and replaced with ciprofloxacin. On 8 March 2002, while still taking his antituberculous medications (viz. ethambutol, ciprofloxacin, and rifampin), he presented with the sudden onset of left-sided limb weakness, headache, diplopia, nausea, and vomiting. MRI showed a new 5-mm enhancing nodule in the left sylvian fissure with leptomeningeal enhancement and evidence of right upper pons ischemia. CSF was now PCR and culture positive for *M. tuberculosis*, with the same patterns of drug susceptibility as the original spinal and urine isolates (Table 1). Isoniazid and pyrazinamide were restarted, ethambutol and rifampin were continued, and the ciprofloxacin dose was increased. Once again he responded clinically with neurological improvement and continued on five-drug therapy. Nine months from presentation (April 2002), his visual acuity declined due to optic neuropathy due to ethambutol, and it was stopped.

On 10 September 2002, he was readmitted to hospital with headache, fever, and abnormal liver function tests. He was intermittently confused and had one generalized seizure. MRI

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TABLE 1. Microbiological and antimicrobial history^a

Date ^b	No. of mos from presentation	Microbiological history				Antimicrobial treatment (total daily dose [mg]) ^c
		Site	Pathology/clinical chemistry result(s) ^c	Culture result	Drug susceptibilities	
08/14/01	0	Spine	Granulomatous inflammation	<i>M. tuberculosis</i>	Susceptible: RIF, E, PZA, S; resistant: INH	
08/14/01		Urine	No AFB	<i>M. tuberculosis</i>		
08/15/01						RIF (600), INH (300), E (1,000), PZA (1,500)
08/28/01		Wrist	Granulomatous inflammation	No growth		
10/04/01						RIF (600), E (1,000)
10/19/01	2	CSF	WBC, 51 × 10E6/liter; protein, 1.32 g/liter; no AFB	No growth		RIF (600), E (1,000), PZA (1,750)
01/25/02	5					RIF (600), E (1,000), CIP (500)
03/08/02	7	CSF	WBC, 89 × 10E6/liter; protein, 0.68 g/liter; no AFB; TB PCR positive	<i>M. tuberculosis</i>	Susceptible: RIF, E, PZA, S; resistant: INH	INH (300), PZA (1500), RIF (600), E (1,000), CIP (1,500)
09/13/02	13	Urine	No AFB	No growth		
09/13/02		CSF	WBC, 960 × 10E6/liter; protein, 0.83 g/liter; no AFB; TB PCR positive	<i>M. tuberculosis</i>	Susceptible: E, S, AMIK, CAP, CYC, CIP; resistant: INH, RIF, PZA ^d	Intermittent AMIK, INH, RIF, PZA; complicated by toxicities
10/24/02	14					All antituberculous medications stopped
11/10/02	15	Urine	No AFB	No growth		
11/10/02	15	CSF	WBC, 11 × 10E6/liter; protein, 0.83 g/liter; no AFB	No growth		
11/13/02	15					Thrice-weekly intra-V antibiotics
12/04/02						Thrice-weekly Intra-V antibiotics: LVX (750), CYC (500)
12/27/02	16					Twice-weekly intra-V antibiotics: LVX (750), CYC (500)
04/04/03	20	CSF	WBC, 6 × 10E6/liter; protein, 0.61; no AFB	No growth		
05/08/03	21					Weekly intra-V antibiotics: LVX (750), CYC (500)
05/14/03	24	CSF	WBC, 1 × 10E6/liter; protein, 0.41; no AFB	No growth		
08/18/03	24					All antituberculous medications stopped
02/19/04	30	CSF	WBC, 1 × 10E6/liter; protein, 0.22; no AFB	No growth		
03/10/04	31	Hip	Granulomatous inflammation	<i>M. tuberculosis</i>	Susceptible: RIF, E, PZA, S; resistant: INH	
04/08/04	32					MXF (400), AMIK (750), CYC (500), PZA (2,000), RIF (600)
06/04/04	34					MXF (400), RIF (600), PZA (2,000)
08/12/04	36					MXF (400), RIF (600)
11/06/06	63					All antituberculous medications stopped

^a INH, isoniazid; RIF, rifampin; E, ethambutol; PZA, pyrazinamide; S, streptomycin; CYC, cycloserine; AMIK, amikacin; CAP, capreomycin; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; intra-V, intraventricular; WBC, white blood cells; TB positive, positive for *M. tuberculosis*.

^b Month/day/year.

^c CSF protein normal range: 0.15 to 0.45 g/liter. All CSF glucose levels were in the normal range (2.8 to 4.4 mmol/liter).

^d Initially reported as PZA resistant; later tested again and found to be susceptible; result confirmed with sequencing of *pncA* gene.

^e Intra-V antibiotics: LVX, 1.5 mg, increased to 2.0 mg after 10 days; AMIK, 5 mg, reduced to 4 mg after 10 days.

demonstrated increased meningeal enhancement, and CSF grew *M. tuberculosis*, again resistant to isoniazid and now also resistant to rifampin, rifabutin, and pyrazinamide (Bactec MGIT 960). The organism remained susceptible to all other first- and second-line agents. MICs determined by the broth microdilution method in the Bactec 460 were as follows: ami-

kacin, 0.5 mg/liter; ciprofloxacin, 1.0 mg/liter; and levofloxacin, 1.0 mg/liter. Resistance to rifampin was confirmed by PCR amplification and sequencing of the RNA polymerase (*rpoB*) gene; a recognized point mutation at position 526 (T for C) was identified (10).

Early during this rehospitalization, his treatment was compli-

TABLE 2. Levels of drugs in serum and CSF

Drug (dose) and time after administration (h) ^a	Level(s) of drug (mg/liter) ^b							
	LVX		AMIK		CYC		MXF	
	CSF	Serum	CSF	Serum	CSF	Serum	CSF	Serum
LVX (1.5 mg intra-V)								
2	9.16, 11.36	Not detected						
6	2.06, not detected							
24	0.19, 1.41							
48	Not detected, not detected							
LVX (750 mg p.o.)								
2	4.08	9.74						
4	7.00	13.21						
20	4.55	6.59						
24	1.72	5.87						
LVX (2.0 mg intra-V + 750 mg p.o.)								
26/2								
2/4	6.11	17.10						
4/6	15.76	12.03						
22/24	10.75	11.53						
24/24	4.44	6.81						
	4.60	5.38						
AMIK (5 mg intra-V)								
2			43.1, 39.3					
6			17.7, 15.5	<0.8				
24			3.2, 2.1					
48			1.1, 0.8					
CYC (500 mg p.o.)								
2					16.2	38.4		
6					19.9	33.6		
24					16.7, 12.2	25.7, 19.7		
MXF (400 mg p.o.)								
4							1.15	2.56
9							0.78	2.16
24							Trace	0.41

^a LVX, levofloxacin; CYC, cycloserine; AMIK, amikacin; MXF, moxifloxacin; intra-V, intraventricular; p.o., oral. Numbers separated by a shall indicate the times after intraventricular/oral drug administration.

^b Amikacin was measured using the Abbott TDx analyzer using a fluorescence polarization immunoassay; levofloxacin was measured by high-performance liquid chromatography.

cated by drug intolerance, including hepatitis, deteriorating renal function, and hearing impairment. On 24 October 2002, all anti-tuberculous treatment was stopped. We decided to follow a strategy similar to that described in a recent report of a similar case cured with intrathecal amikacin and levofloxacin (4).

On 13 November 2002, an intraventricular Rickham reservoir was surgically inserted to allow administration of intraventricular antibiotics, and a new regimen was started with thrice-weekly intraventricular amikacin and levofloxacin (Table 1) plus oral levofloxacin and increasing doses of cycloserine (to 500 mg daily). When drug levels showed detectable amikacin in the CSF at 48 h and penetration of the CNS by oral levofloxacin and cycloserine, we reduced the intraventricular injection frequency to twice weekly from 27 December 2002 (Table 2). We continued this regimen until 14 May 2003, when we decreased the intraventricular injection frequency to weekly; all medications were stopped on 18 August 2003, a total of 9

months of combined intraventricular and oral therapy (Table 1). During this time he improved, with no further CNS events, and his CSF parameters became normal; the CSF was culture negative 6 months after treatment stopped (Table 1).

He remained well, but in March 2004, he reported left hip pain and an X-ray showed a lucent area adjacent to the femoral shaft of his left hip prosthesis. Fine-needle aspiration (10 March 2004) showed granulomatous inflammation, and *M. tuberculosis* was isolated. Restriction fragment length polymorphism typing of IS6110 showed this and the previous four isolates, including the rifampin-resistant CNS isolate of 13 September 2002, to be indistinguishable (12). The laboratory then reported that the results of pyrazinamide susceptibility testing (Bactec 460) of 10 December 2002 were incorrect; all four isolates were in fact pyrazinamide susceptible. Susceptibility was confirmed by repeating susceptibility testing in the Bactec MGIT 960 (8) in duplicate and sequencing of the *pncA*

gene; no mutations were identified (2). We believe that this erroneous result was due to well-described difficulties with phenotypic pyrazinamide susceptibility testing (8). Initially, because of concern that his multidrug-resistant organism could be responsible for infection in his hip, he began treatment with moxifloxacin, amikacin, cycloserine, rifampin, and pyrazinamide (Table 1). The hip isolate was subsequently shown to be resistant only to isoniazid, a result identical to that for the original isolates. From 4 June 2004, he was treated with moxifloxacin, rifampin, and pyrazinamide, and on 9 July 2004, he underwent the first stage of a two-stage revision with prosthesis removal and insertion of an amikacin-loaded femoral spacer. Granulomatous material was present at the site of the lucent zone, but no *M. tuberculosis* was seen or cultured this time. His immunosuppressive treatment was slowly reduced and then stopped during August 2004, since his underlying lupus was well controlled; on 12 August 2004, his pyrazinamide was stopped, again because of recurrent gout. He continued rifampin and moxifloxacin as his definitive treatment until 6 November 2006, with the second stage of his total hip joint replacement revision done 4 months before treatment completion. He remains well, without recurrence of tuberculosis, 20 months (June 2008) after stopping treatment. He was always compliant with his medicines.

As described herein, we isolated *M. tuberculosis* five times over a 32-month period from our patient's urine, spinal tissue, CSF (twice), and hip tissue. Restriction fragment length polymorphism analysis confirmed clonality despite the changed susceptibilities of the 13 September 2002 CSF isolate. Amplification and sequencing of the *rpoB* gene in all isolates confirmed rifampin resistance only in that CSF isolate. We assume that inadequate concentrations of antituberculous medications in his CNS due to interruptions in therapy and poor CNS penetration resulted in selection of a rifampin-resistant mutant of his initial *M. tuberculosis* strain and that his immunocompromised state allowed this organism to proliferate.

The later occurrence of prosthetic hip joint infection due to the original isoniazid-resistant, rifampin-susceptible strain initially surprised us. We presume that dissemination of infection to the prosthetic femoral shaft site occurred before the relapse of CNS infection due to the rifampin-resistant isolate, possibly at the time of his initial presentation with multifocal disease. Infection persisted at this site despite his prolonged treatment course, which successfully cured isoniazid-resistant disease in the known extra-CNS sites. Prosthetic joint infections due to *M. tuberculosis* are sometimes cured without prosthesis removal using standard regimens, but more often they fail (3, 11), so it is not altogether surprising that a focus of infection remained in this periprosthetic location.

Use of the Rickham reservoir for intraventricular antibiotic administration afforded an opportunity to measure levels of antibiotics in the CSF (4, 6, 7). We confirmed that intraven-

tricular amikacin persisted in the CSF for more than 48 h and levofloxacin for more than 24 h. Oral levofloxacin (750 mg) penetrated well into the CSF and persisted for more than 24 h, while oral moxifloxacin (400 mg) entered relatively less well. We confirmed oral cycloserine's excellent CSF penetration (5). These data enabled us to confidently devise an individualized regimen which ultimately sterilized his CSF. These levels add useful data to the literature (4, 6) for others managing multidrug-resistant *M. tuberculosis* meningitis in a period of increasing prevalence of antituberculous drug resistance (1).

The later definitive regimen of surgery with continuing moxifloxacin and rifampin was successful for his prosthetic infection, a regimen supported by clinical studies (9).

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