Clinical Case Report

Multidrug-resistant tuberculosis in an HIV-infected girl

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ABSTRACT
Multidrug-resistant tuberculosis (MDR-TB) in patients with human immunodeficiency virus (HIV) infection poses multiple challenges for treatment, and has a high mortality. MDR-TB coinfection in children, though such coinfection has been reported in adults, is rare. A 9-year-old HIV-infected girl requiring antiretroviral therapy (ART) developed MDR-TB and responded to second-line antituberculous therapy.


INTRODUCTION
Multidrug-resistant tuberculosis (MDR-TB) coinfection with human immunodeficiency virus (HIV) is an emerging health problem in India.1 In a study from Chennai, 4.42% of adults infected with MDR-TB were reported HIV-seropositive.2 However, no HIV-infected child has been reported to have MDR-TB in India. According to the fourth WHO report on antituberculosis drug resistance, MDR-TB has been shown to be almost twice as common in patients with HIV infection than in those without HIV. Also, the case-fatality rate with MDR and extensive drug-resistant TB (XDR-TB) is as high as 90% in people living with HIV.3 This is exemplified in a case series of 287 patients with TB from Peru. In this study, 98% of TB mortality was associated with AIDS and 55% of MDR-TB patients with AIDS died within 2 months of diagnosis.4 We present the case of a 9-year-old HIV-infected girl requiring antiretroviral therapy (ART), who developed MDR-TB and responded to second-line antituberculous therapy (ATT).

THE CASE
A 9-year-old HIV-infected girl presented in June 2006 with fever for 7 months and dry cough for 10 days. Both her parents were HIV-infected and her father had died of TB 5 years ago. She was on ATT for the past 10 months, which had been started by her treating physician for non-resolving pneumonia. Sputum examination 4 months ago was negative for acid-fast bacilli (AFB). On examination, she was 125 cm tall and weighed 20 kg (body mass index 12.8 kg/m²). She had oral thrush and bilateral diffuse crepitations on respiratory system examination. Other systems were normal. Her haemoglobin was 10.9 g/dl and white blood cell count was 4800/cmm (64% polymorphs, 35% lymphocytes) with a platelet count of 325 000/cmm. Her X-ray chest showed right-sided calcified primary complex. Her alanine aminotransferase was 29 IU/L, serum amylase 19 IU/L and CD4 count was 36 cells/cmm (1.69%). She was started on azithromycin and cotrimoxazole prophylaxis. ATT was stopped. She was also started on three-drug ART consisting of zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP).

A month later, she had fever with cough. Sputum smear examination was positive for AFB and a chest X-ray showed left lower zone consolidation. She was then started on six-drug ATT consisting of isoniazid (INH), rifampicin, ethambutol, pyrazinamide, streptomycin and ciprofloxacin. NVP was increased to 400 mg/m²/day. Subsequently, she developed NVP-induced maculopapular rash and NVP was replaced with efavirenz. Culture of sputum after 6 weeks grew Mycobacterium tuberculosis resistant to streptomycin, INH, rifampicin and ethambutol. The bacteria were sensitive to pyrazinamide, kanamycin, ethionamide, para-aminosalycic acid (PAS) and ofloxacin. Treatment under the directly observed treatment, short-course (DOTS) programme was suggested but the mother wished to continue treatment at our centre.

The child was started on alternate ATT consisting of kanamycin (15 mg/kg/day for 2 months), PAS (150 mg/kg/day in divided doses for 3 months), ethionamide (15 mg/kg/day for 8 months), pyrazinamide (30 mg/kg/day for 2 years) and ofloxacin (16 mg/kg/day for 2 years). Every month her growth was assessed and a haemogram and biochemical tests were done. Chest X-rays were done every 3 months. Her sputum smear became negative after one month of therapy. Repeat cultures were not done since the child had stopped producing sputum. In November 2006, her weight had increased to 24 kg. However, on regular screening for adverse effects, she was found to have hypothyroidism (T3 1.3 ng/dl, T4 60 mg/dl, TSH 7.5 mIU/ml). She was started on 25 mg of levothyroxine once a day. In December 2006, her CD4 count increased to 77 cells/cmm, in June 2007 it increased to 170 cells/cmm and in January 2008 it increased to 304 cells/cmm. Azithromycin prophylaxis was stopped in December 2006. Her chest X-ray done in February 2008 was normal. As her thyroid function tests remained normal, thyroxine was tapered and stopped. She had a weight gain of 10 kg in 18 months (weight in February 2008 was 30 kg) and was tolerating ART well. Pyrazinamide and ofloxacin were stopped at the end of 2 years.

DISCUSSION
Treatment of TB and HIV coinfection is complicated by various factors including drug resistance, drug interactions and drug toxicity, as seen in this patient who was in WHO Clinical Stage III of HIV. The child, already on three-drug ART, was started on first-line ATT when she was sputum AFB-positive. Six weeks later, TB culture and drug susceptibility results showed the strain to be MDR, i.e. resistant to most of the first-line drugs including INH and rifampicin. Conventional culture, the most common method of detecting drug resistance in developing countries, has the inherent problem of a delay in diagnosis varying from 6 weeks to 3 months. A more rapid detection of drug-resistant TB is desirable in populations with a heavy burden of MDR-TB or coinfection with HIV in order to reduce the time spent on...
ineffective treatment and to decrease mortality.\textsuperscript{1,4} A history of previous treatment for TB is a useful predictive factor for MDR-TB in a cohort of HIV-infected patients with TB.\textsuperscript{1} One must also keep in mind that immune reconstitution in the setting of recent initiation of ART may unmask drug-resistant TB and hence timely empirical MDR-TB treatment is important in suspected cases.\textsuperscript{8}

In children with HIV infection, treatment of MDR-TB is extended to 24 months\textsuperscript{8} and an individualized treatment regimen is required. The principles of management of resistant disease include use of aggressive regimens for protracted periods, guided by drug susceptibility testing to include at least five drugs likely to be effective.\textsuperscript{10} Fluoroquinolones play a key role in resistant TB and the later generation fluoroquinolones may be effective despite resistance to ciprofloxacin. Use of an injectable agent such as capreomycin or an aminoglycoside (e.g., kanamycin), have been shown to predict culture conversion and survival.\textsuperscript{11} However, resistance to more than one aminoglycoside is becoming increasingly common. The regimens may be reinforced by pyrazinamide and ethambutol despite prior exposure to these drugs, as these contribute by increasing the regimen’s activity or preventing resistance to more active agents. An oral quinolone is generally continued for the duration of therapy, in combination with another agent such as ethambutol (or pyrazinamide in this case) for 18 months after smear ‘conversion’.

Common adverse effects of second-line ATT include gastrointestinal effects, rash, ototoxicity, peripheral neuropathy, psychiatric symptoms and jaundice. The rate of thyroid toxicity is high,\textsuperscript{12} and may be due to ethionamide or PAS, requiring regular monitoring. Besides, serial CD4 levels, monitoring of liver function tests, lipid profile and pancreatic enzymes is essential for a child receiving ART.

A delay in laboratory diagnosis, limited choice of active drugs and increased toxicities and interactions when ATT and ART are simultaneously administered, all contribute to making the treatment of MDR-TB with HIV a challenging task. It calls for individualization of treatment and adjustments in drug regimens from time to time.

REFERENCES


